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July-August
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ANNALS of ALLERGY

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THE TECHNIQUE OF RESPIRATORY AND PHYSICAL EXERCISE IN THE TREATMENT OF BRONCHIAL ASTHMA

BERNARD T. FEIN, M.D., F.A.C.A., and EUGENIA P. COX, B.A.
San Antonio, Texas

IN RECENT YEARS, the importance of supervised respiratory and physical exercise as a means of improving respiration in bronchial asthma has been recommended by numerous investigators.[1-3,5-9] A short time ago, one of these men[6] complained that this type of therapy had not been stressed sufficiently enough to be accepted by physicians in the United States. Many of us have found that even the extensive use of ACTH and cortisone has not altered the progressive pathologic changes which occur in bronchial asthma. These underlying changes, which eventually result in incapacitating pulmonary emphysema even under the best used therapies, must be overcome by all available means.

This type of treatment which is readily available should be employed whenever and wherever possible. The purpose of this paper is to present the exact routine and techniques of respiratory and physical exercises used. These exercises have been previously outlined by the Asthma Research Council, of London, England.[1]

EQUIPMENT AND PERSONNEL

A nurse or physiotherapist to educate the patient is employed. An examining table, straight back chair, and a wide belt is needed. The ex-

From the Allergy and Physical Therapy Clinics, Department of Medicine, Veterans Administration Regional Office, San Antonio, Texas.

Dr. Fein is Chief of the Allergy Clinic, Veterans Administration Regional Office, San Antonio, Texas, and Consultant in Allergy, U.S.A.F. Base Hospital, Lackland A.F.B., San Antonio, Texas.

Mrs. Cox is Chief of the Physical Therapy Department, Veterans Administration Regional Office, San Antonio, Texas.

Presented at the Eleventh Annual Congress of the American College of Allergists, Chicago, Illinois, April 28, 1955.

pansometer, chest caliper, and a vital capacity apparatus are ideal for measuring progress, but not entirely essential.

METHOD

On the first visit, the patient is given an orientation lesson. When the

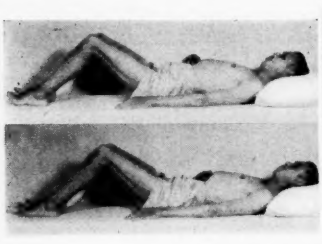

Fig. 1.

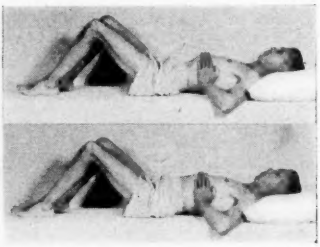

Fig. 2.

Fig. 1. Diaphragmatic breathing exercise, lying.
Fig. 2. Side expansion breathing exercise.

general idea of what the exercises are to accomplish is understood, the patient is taught Exercises 1, 2, and 5.

On the second visit, the assigned exercises which were practiced at home are reviewed and Exercises 3, 4, 6, and 7 are taught.

On the third visit, assigned exercises are again reviewed, a record is made of the chest measurements by means of the expansometer and chest calipers, and the vital capacity is recorded.[5-12]

On subsequent visits, assigned exercises are reviewed, and exercises 8, 9, 10, 11, and 12 are taught. The progress depends entirely on the ability of the patient to grasp the exercises and tolerate them. The exercises are performed at home for ten-minute periods, before breakfast, lunch, bedtime, and at the onset of an asthmatic paroxysm.

SPECIFIC METHODS

Elementary Exercises.

1. *Diaphragmatic Breathing Exercise—Lying (Fig. 1).*—The position is on the back with the knees bent, feet on bed, completely relaxed. The hands are placed on the abdomen on the lower ribs.

The exercise consists of three parts: breathing out slowly making the chest as small as possible and tightening the abdominal muscles, relaxing the abdominal muscles and breathing in quickly through the nose, and then breathing out quickly through the nose and mouth, again tightening the abdominal muscles.

2. *Side Expansion Breathing Exercise (Fig. 2).*—The position is on the back with the head and shoulders resting on pillows with the hands

placed on the lower ribs and the knees bent. The exercise consists of breathing out through the mouth and slowly making the chest smaller and then giving a final squeeze with the hands, then breathing in through the nose and pushing the lower ribs out against the pressure of both hands, relaxing the pressure at the height of the insipration but not moving the upper chest.

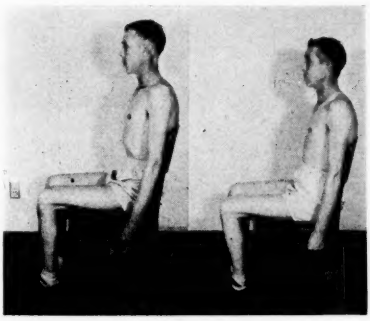

Fig. 3.

Fig. 4.

Fig. 3. Diaphragmatic breathing exercise, sitting.
Fig. 4. Side expansion breathing exercise with belt for pressure.

3. *Diaphragmatic Breathing Exercise—Sitting (Fig. 3).*—The position is sitting with the back resting against a chair, completely relaxed. The patient breathes out slowly, sinking in the chest and tightening the abdominal muscles, then relaxing the abdominal muscles while breathing through the nose.

4. *Side Expansion Breathing Exercise with Belt for Pressure (Fig. 4).*—The position is sitting in a chair with back supported. A wide belt is placed around the lower ribs above the waist. The crossed ends of the belt are grasped by the patient. Breathing is started by blowing out slowly and allowing the chest to become smaller. When all the air is out, the ribs are squeezed a little by tightening the belt. The lower ribs are then expanded against the belt easing up the pressure at the end, as the patient quietly breathes through the nose.

5. *Elbow Circling Exercise (Fig. 5).*—The position is sitting in a chair, leaning forward with the back straight. The fingertips are placed on the shoulders, elbows are bent and out to the side, in line with the shoulders. There is a circling of the elbows up, back, and down, the four circles are performed, then relaxing.

6. *Forward Bending Exercise (Fig. 6).*—The position is sitting with the feet apart and arms relaxed at the sides. The patient breathes out

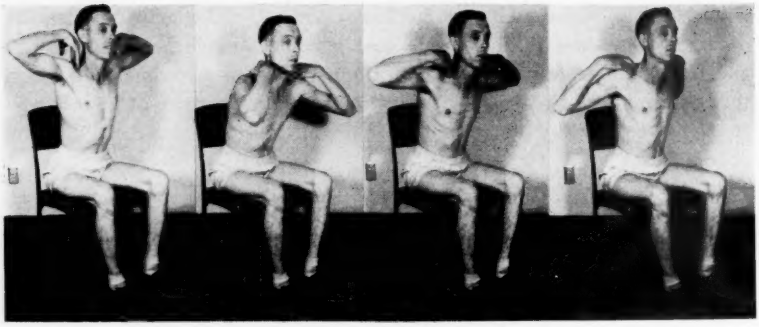

Fig. 5. Elbow circling exercise.

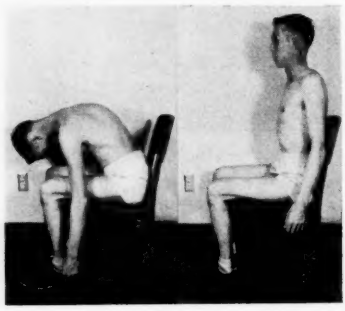

Fig. 6.

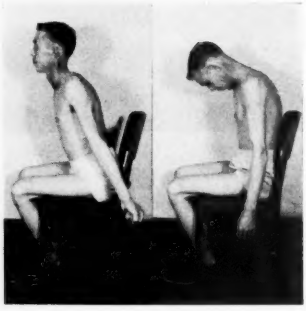

Fig. 7.

Fig. 6. Forward bending exercise, sitting.

Fig. 7. Relaxing exercise.

slowly as he bends forward, first the head, then the shoulders, until the head almost touches the knees. The abdominal muscles are tight. The body is gradually raised, by first pushing the lower back against the chair, then the middle and upper back, shoulders, neck, and head, breathing in as the upper back is straightened, and relaxing the abdominal muscles, keeping the back and head erect. Small breaths should be taken, expanding the lower ribs and relaxing the abdominal muscles.

7. *Relaxing Exercise (Fig. 7).*—The position is sitting in a chair. Leaning forward, the patient presses the back of the head, neck, arms, and shoulders to the count of two. Then he relaxes, dropping the head and arms and allowing the back to round out to the count of four.

Advanced Exercises.

8. *Abdominal Muscle Exercise (Fig. 8).*—The position is lying on back with the knees bent and feet on the bed, keeping the arms and the

shoulders relaxed. The right knee is slowly raised to the chest while breathing out and tightening the abdominal muscles. The patient should then pause in breathing, lowering the right knee; then breathe in, relax the abdominal muscles, and gently expand the lower ribs only. This is

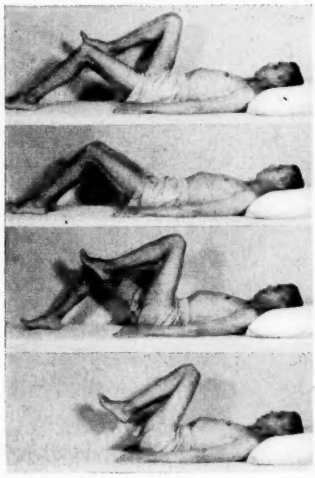

Fig. 8. Abdominal muscle exercise.

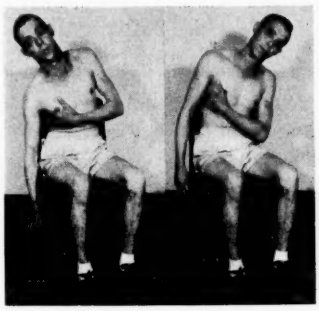

Fig. 9. Side bending exercise.

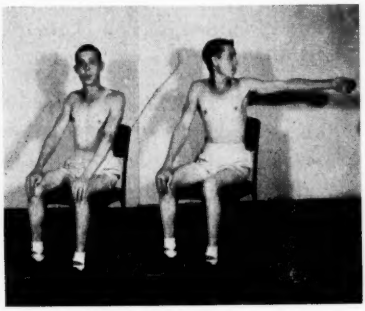

Fig. 10. Trunk turning exercise.

repeated for the left knee, and repeated again bringing both knees to the chest.

9. *Side Bending Exercise (Fig. 9).*—The position is sitting with the feet apart with the right arm relaxed at the side and the left hand placed over the sides of the right middle ribs. While breathing out, the patient bends the head and shoulders to the right and presses the hand against the

side, bending the head and shoulders to the left slightly while breathing in, and swelling the right lower ribs as much as possible to the right. This part of the exercise is done quicker than the first part. After six bends to the right, a change is made to the left and six more bends are made.

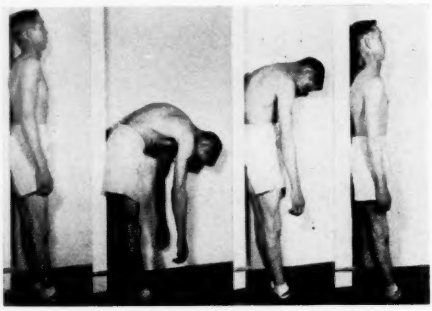

Fig. 11. Forward bending exercise, standing.

10. *Trunk Turning Exercise (Fig. 10).*—The position is sitting with the feet apart and the hands on the knees. The back is kept straight without leaning forward. The twisting is done from the waist up. The patient turns the body and flings the left arm sharply to the left, turning the trunk as far as possible, so that the left shoulder is back, the right forward, and the head turned to look at the palm of the hand. After relaxing he should turn back to the starting position, and repeat, turning to the right.

11. *Forward Bending Exercise (Fig. 11).*—The position is standing with the back, shoulders, and head against a wall and the feet about six inches from the baseboard. The patient breathes out as he bends down slowly, dropping first the head, then the shoulders, the upper back, and finally, the lower back. The arms are hung limply and the abdominal muscles are tight. Then he must straighten up, keeping the abdominal muscles tight, and flatten the lower back against the wall, relaxing the abdominal muscles to breathe in as he straightens the rest of the back gradually. He must hold the upper back and head against the wall and breathe out quickly by tightening the abdominal muscles, forcing the low back against the wall. A small breath is taken before repeating the exercise.

12. *Side Bending Rotation Exercise (Fig. 12).*—The position is standing with the feet apart. The arms are brought above the head as the patient breathes in. Then he bends slowly to the left as far as possible while breathing out, letting the arms bend loosely at the elbows. While bending the body is twisted so the arms are fully carried outside of the

left foot, while continuing to breathe out. The body is raised upright, with the arms overhead as he breathes in. The exercise is repeated to the right.

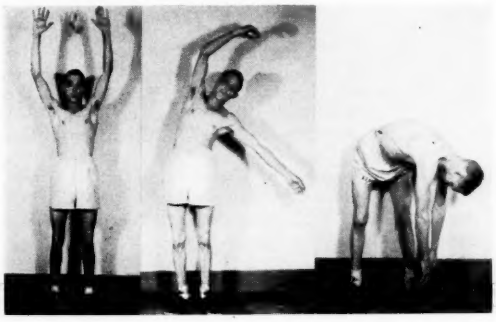

Fig. 12. Side bending rotation exercise.

EVALUATION OF RESULTS

Measurements[5,11,12] are done by using the expansometer and the chest caliper. This device measures both halves of the chest simultaneously in order to determine the excursion of each side, revealing the lack of movement of each half. The chest caliper, which is a standard pelvimeter modified for the purpose, accurately measures the movements of the upper segments of the chest.[5,11,12] A vital capacity apparatus of any type available is used to record the lung capacity.

DISCUSSION

These exercises have been advocated as a supplementary measure in the treatment of bronchial asthma. The regular allergic and medical therapies should not be interrupted during the educational period. Where mechanical devices for improving respiration, such as the intermittent positive-pressure apparatus,[10] the repetimeter,[13] and the exsufflator,[4] are available, they should be utilized to the fullest benefit. All treatments which will prevent the widening of the costal angles, and the over-distention of the chest should be used. We have used these exercises, in private patients, after only a short educational period, and the results have been gratifying. After only four years of the employment of physical exercise, we feel that they require willing students if they are to be of therapeutic and prophylactic value. Ability to master the controlled breathing, to the point of being able to abort mild attacks of asthma, depends upon the individual and the diligence of the physician.

SUMMARY

1. The equipment, personnel, and method of employing respiratory and physical exercise in the treatment of bronchial asthma is presented.

2. The specific methods of instruction are outlined together with means of evaluation.

3. The success of this method of treatment depends not only on the patient's ability, but on the allergist's recognition of their value and application.

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1422 Nix Professional Building (Dr. Fein)

CONFERENCE ON VASCULAR HEADACHES HELD AT NEW ENGLAND MEDICAL CENTER

A conference devoted entirely to the causes, diagnosis, and treatment of vascular headaches was held at the New England Medical Center on May 5, 1955. Dr. Derek E. Denny-Brown, professor of neurology at Harvard Medical School, served as moderator and also discussed the differential diagnosis of headache. Other speakers on the panel were Dr. Bertram Selverstone of Tufts Medical College, Dr. John R. Graham of Harvard Medical School, Dr. Bayard T. Horton of the Mayo Clinic, and Dr. Arnold P. Friedman, director of the headache clinic of Montefiore Hospital in New York. Their addresses covered the neurosurgical aspects of head pain, mechanisms of vascular headache, and the diagnosis and treatment of migraine, tension, and histamine headaches. Proceedings of the conference will be published in the Bulletin of Tufts-New England Medical Center. A film presenting the views of the speakers is being prepared for showing to medical groups throughout the country, and physicians interested in viewing it should contact the film division of Organon, Inc., Orange, New Jersey.

THE VALUE OF BRONCHOSCOPY IN ASTHMA

JOSEPH D. HOWELL, M.D.
Indianapolis, Indiana

BRONCHOSCOPY is employed in bronchial asthma for a variety of reasons. In the majority of cases this procedure is carried out for the purpose of breaking up an intractable state of asthma which does not yield to other modes of therapy. The removal of mucus from the bronchial tree itself may give relief from an asthmatic attack. The removal of a single mucous plug which caused either complete or partial atelectasis of a pulmonary lobe may be accomplished by it and thus end the asthmatic attack. Patients with bronchostrictures of inflammatory origin may show complete recovery following a single bronchoscopic dilatation of the strictures. The results have been well documented by Waldbott.[1,2]

Bronchoscopy may also be performed for the purpose of collecting secretion for complete bacteriologic study. An autogenous vaccine may be made for hyposensitization treatment.

There are many cases of asthma and, particularly, many patients with a cough in whom this procedure is a valuable diagnostic aid in determining if the symptoms are entirely allergic in origin. The patient may have some other conditions which is aggravating the asthma. Any severe case of asthma which does not respond to other therapy, or a patient who has a cough and does not have a typical allergic history, should have the benefit of a diagnostic or therapeutic bronchoscopy. It is the only method whereby the tracheobronchial tree can be surely and carefully examined. In the course of the examination one can observe the appearance of the mucous membrane and the caliber and contour of the trachea and of both main bronchi, searching for evidence of intrinsic growth or extrinsic compression, altering the size of the lumen. In addition, the general conformation of the openings of the bronchial branches to the different lobes may be observed relative to the presence or absence of organic changes, such as thickening, fixation and displacement. Likewise, the presence of abnormal tissue or secretion and other details may be noted in localizing and identifying abnormal changes. Bronchoscopy has certain limitations in that one is unable to see lesions distal to points of direct view, and in these cases additional valuable information may be obtained by the use of telescopes and pneumonography.

While there is no attempt in this paper to present any new material, it is often very important to re-emphasize what has been known in the past. The following cases represent what can be found at bronchoscopy in the practice of allergy.

Presented at the Eleventh Annual Congress of the American College of Allergists, Chicago, Illinois, April 28, 1955.

Dr. Howell is an Associate Fellow of the American College of Allergists.

CASE HISTORIES

Case 1.—A nine-year-old boy gave a past history of frequent head colds followed by a cough. These had been present all his life and occurred mostly in the winter. He was seen in the office in December, 1951, having had a non-productive cough of two months duration. There was no family history of allergic diseases. Ascultation of the lungs revealed no wheezes or rales. Fluoroscopy and x-ray of the lungs showed a homogeneous density occupying the right middle lobe and the x-ray interpretation was atelectasis of the right middle lobe. At bronchoscopy the middle lobe orifice was found to be red and about one-half its normal caliber. Aspiration and irrigation were performed. An x-ray of the chest two months later showed only slight haziness in the region of the right middle lobe, and follow-up studies showed no cough for two years following the bronchoscopy.

Case No. 2.—A thirty-seven-year-old man had a history of asthma of fifteen years' duration. He had received hyposensitization treatment with pollen, dust and molds with good results. In July, 1952, he developed pneumonia. An x-ray showed pneumonic consolidation of the left lower lung. An x-ray of the chest a week later showed the process to be resolving, and he soon became symptom free. In October, 1952, he again developed a fever and cough. X-ray of the chest revealed irregular parenchymatous densities, which had more the appearance of fibrosis or slight peribronchial inflammatory changes in the inner and middle zones of the lower third of the left lung field. This was exactly the same site as the previous pneumonic process. Bronchoscopy revealed a large amount of purulent secretion in the left lower lobe. The mucosa demonstrated marked redness, some edema and thickness, and about 50 per cent narrowing of the lumen. Lipiodol instillation two weeks later showed almost complete atelectasis of the left lower lobe, but the left upper lobe filled normally. A spot film showed cystic bronchiectasis of the left lower lobe segments; therefore, a month later a partial left lower lobectomy was performed. The patient's cough disappeared.

Case No. 3.—A sixty-five-year-old woman was seen in a hospital in January, 1950 with a history of asthma since childhood. For the past four years she had very severe coughing and wheezing attacks whenever she developed an upper respiratory infection. Her cough had been productive of yellow sputa the past four years.

X-ray of the chest showed marked contracture of the right upper lobe area with numerous small and medium sized cystic cavities. There were numerous calcific densities about the peritracheal area and in the parenchyma of the lung. There were many infiltrative densities and smaller cystic areas seen in the right lower lung field. The trachea, heart and mediastinal structures were all pulled to the right.

At bronchoscopy the trachea was directed to the right. The mucosa of the left main bronchus showed thickening and ridging due to chronic inflammatory changes. A large irregular calculus was removed from the left lower lobe bronchus. The right main bronchus was almost entirely obstructed by a calculus which was removed. Re-examination of the right main bronchus after removal of the calculus demonstrated a small orifice through which a spring aspirator could be passed into the lower lobe. It was thought that the middle lobe orifice was completely occluded by more calculus.

The patient was again bronchoscoped two weeks later. No more calculi were removed. The stricture in the right main bronchus was still present. Purulent secretions were removed from the right upper and lower lobes. A biopsy was performed. Impression of the bronchoscopist was that of stricture and marked bronchiectasis of the right lung.

Tissue examination of the biopsy showed non-specific bronchitis and epithelial hyperplasia. Sputa studies were negative for tubercle bacilli.

After the bronchoscopies this patient's asthma was much better. She still had upper respiratory infections with coughing but very little wheezing. X-ray of the chest three years later showed about the same findings.*

Case No. 4.—A forty-eight-year-old man was seen in the office in November, 1953. He had had a cough for the past twenty years, and developed asthma four years ago. It was noticed in the office that his cough was of the severe brassy type; however, x-ray of the chest was normal. Bronchoscopy showed a bulge in the mid portion of the trachea on the right side. There was also some obstruction of the mouth of both the right and left main bronchi. Planogram films of the chest suggested that a mass was impinging on the trachea. At surgery it was found that there was a fairly large nodule in relationship to the right lobe of the thyroid which surrounded about two-thirds of the circumference of the trachea primarily on the right side. Because of the adhesions present it was necessary to completely remove the right lobe of the thyroid. The left lobe of the thyroid was palpated and found to be normal. The patient's brassy cough disappeared, although he continued to wheeze.

Case No. 5.—A fifty-five-year-old man was first seen in his home in March, 1954. He gave a history of having had a morning cough for the past six years, which was productive of a yellow mucus. He developed asthma about two years previously. Because of poor response to oral medication, he was hospitalized. X-ray showed only increase in peribronchial markings and emphysema in both lower lobes. Bronchoscopy showed the right bronchial tree to be almost completely filled with mucopurulent exudate and there was very little air exchange on inspiration. The left main bronchus demonstrated moderate fixation on inspiration and typical respiratory asthmatic contraction. Impression was that of very severe emphysema with almost no air exchange. Bronchoscopy gave very little relief of respiratory distress. It was not until after he received daily penicillin injections for a week that he showed improvement in breathing. When seen in the office his best vital capacity was 1.2 liters, or 28 per cent of normal. He did fairly well until October, 1954, when he developed an upper respiratory infection and his breathing again became very labored. He soon developed rales in the right lower lung base, enlargement of the liver, and ankle edema. Administration of Thiomerin® and digitalis was of no avail. He was hospitalized and again bronchoscoped. A large amount of rather thick mucoid material was removed and the same amount of emphysema was noticed. Within two days the findings of cardiac insufficiency disappeared. In February, 1955, he again developed an upper respiratory infection and severe respiratory distress. Bronchoscopy failed this time to relieve any of his symptoms. In spite of treatment for the cardiac insufficiency he developed acute pulmonary edema and died. An autopsy was not obtained.

Case No. 6.—A fifty-five-year-old widow gave a history of asthma of two years' duration. There was a positive familial history for allergy. X-ray of the chest was normal. Observations suggested that psychophysiologic factors played an important role in her symptomatology. She continued to have poor response to therapy and was bronchoscoped. This revealed much redness of the mucosa of the entire left bronchial tree. In the region of the left upper lobe orifice the mucosa was laid in ridges. The lumen of the left lower lobe was about one half its normal caliber. There was good motion on respiration and no restriction noted in air exchange.

*This case was presented through the courtesy of Dr. Thomas Johnson, Indianapolis, Indiana.

There was expiratory contraction compatible with asthma. While this patient continued to have asthma afterward, not all of it was due to a psychophysiologic basis.

SUMMARY

Many asthmatic patients respond poorly to allergic management. Other patients have symptoms which are not entirely explained on the basis of their allergic disease. These patients should be bronchoscoped because certain mechanical factors may be discovered which may account for poor response to therapy. Six representative cases have been presented.

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760 Bankers Trust Building

CONFERENCE ON ACTH HELD BY ACADEMY OF MEDICINE OF NEW JERSEY

The Academy of Medicine of New Jersey held a special conference on ACTH on April 28, 1955, in Newark. Dr. Philip S. Hench of the Mayo Clinic was moderator for this symposium, and the guest speakers included Dr. Peter H. Forsham of the University of California Medical School, Dr. John C. Laidlaw of the University of Toronto Medical School, Dr. Heinrich G. Brugsch of the New England Medical Center, Dr. Harry E. Banghart of Hahnemann Medical School, and Dr. Bram Rose of McGill University Medical School. The subjects under discussion were the physiologic and clinical effects of various corticotropins (including a discussion of a new type of long-acting ACTH), special uses of corticotropin in diagnosis and stress, the present status of corticotropin therapy in the management of rheumatic diseases, corticotropin therapy in other collagen diseases, and therapy with corticotropin in allergic and hypersensitive states. A film giving the views of the speakers will be prepared for showing to medical groups throughout the country. Physicians interested in viewing it should contact the Academy of Medicine of New Jersey, 91 Lincoln Park South, Newark, N. J. The *Academy of Medicine, New Jersey, Bulletin* will contain the proceedings of this conference in an early issue.

ASTHMATIC BRONCHITIS

A Follow-Up Study in a General Pediatric Practice

GEORGE A. WATSON, M.D., F.A.C.A.
Durham, North Carolina

AS a diagnostic term, the use of "asthmatic bronchitis" is in frequent use in the pediatric nomenclature; but as to the ultimate outcome of patients to whom this diagnosis has been applied, little has been written.

A recent paper on "The Composition of an Average Pediatric Practice"[1] afforded an opportunity to do follow-up studies on a group of children, who in the course of study have been diagnosed as having this disease entity. The original study analyzed 1500 consecutive cases and tabulated these as to presenting diagnosis. This report, then, has to do with a series of twenty-three patients who were diagnosed as having asthmatic bronchitis during the period of five years that the study covered. Of the number originally reported, three cases were discarded because adequate follow-up studies were not possible. In eleven cases the diagnosis was made during the child's hospital stay. The remainder were so diagnosed during office visits. All of these cases represent patients who have been followed over a period of years, and, in most instances other siblings have been followed in routine pediatric care.

The term "asthmatic bronchitis" itself calls for some clarification, although descriptive summaries are given in the standard pediatric texts. Rubin[2] describes "asthmatic bronchitis" in Nelson's *Textbook of Pediatrics* and cautions that it is important to determine whether these cases represent instances of respiratory infection in asthmatic children during an attack of asthma or whether they represent wheezing in a non-atopic child with bronchitis. Differential factors in separating the two classifications are listed as: (1) the presence or absence of eosinophilia; (2) the presence or absence of a personal or a familial history of allergy; and (3) the response to epinephrine.

In no case was this diagnosis applied to any child where there was a known allergic background or in any instance where previous allergic stigma (eczema, urticaria, et cetera) had been known or observed. The presence or absence of eosinophils in the smear of peripheral blood was not of clinical significance since these patients were, for the most part, less than a year old, and represent an age group where this response is not consistently present.

As to the effectiveness of epinephrine and its reliability as a means of differentiating between asthma and asthmatic bronchitis, I can say little. Primarily, we were not particularly concerned with that dilemma, for these

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cases were such that we were rather convinced that the children did not have asthma. In four of the hospitalized cases epinephrine was given at the direction of the house officer. In three of these cases progress notes show that there was no response. In one case respiratory improvement was noted with diminishing wheezing after epinephrine was administered.

It is apparent that further delineation is necessary. Admittedly, this is a somewhat nebulous subject but, briefly, these patients presented the following clinical picture. They were all small children and most of them were infants. Wheezing respirations, coughs and fever were consistent. Despite this, however, none of them seemed acutely ill, and the lack of severe respiratory distress and prostration separated them from cases of bronchiolitis. Each family was carefully questioned about the possibility of a foreign body or aspiration pneumonia. In every case where this possibility was seriously considered x-rays were taken for confirmatory evidence. In one child with a suspiciously high white count, the diagnosis of peritussis was considered; however, cough plates and subsequent counts proved this to be untrue.

A more detailed survey of the diagnostic criteria employed in establishing a diagnosis of asthmatic bronchitis is listed in Table I. They deserve a more critical analysis.

TABLE I

	Asthmatic Bronchitis	Asthma
Fever	++ to ±	±
Uniform Musical Rales		+
Inspiratory Rhonchi and Rales, Musical Rales	+	0
Epidemic	+	0
Leukocytosis	+	0 to ±
Eosinophilia	0	+
Family History of Allergy	±	+
Cough	+++	+

Fever.—An elevated temperature was consistently present and averaged between 100 and 101 degrees. Admission temperature ranges were found between 99 and 105 degrees, but these cases were exceptions with the great majority being in the mean range. This elevation then is in contrast with the known asthmatic state in which fever is uncommon and even when present is lower.

Chest Findings.—Wheezing respirations were shown in the inspiratory as well as expiratory phase of respirations. Usually this was audible and frequently served as the chief concern on the parents' part. Breath sounds were harsh about the hilar area, and fine musical rales were noted along the course of the descending bronchi.

Leukocytosis.—While moderate, this was consistently higher than the expected findings in true asthmatic patients. Average counts ranged about

10,000, but one infant had an elevated count of 27,300. A relative lymphocytosis, even for this age group, was a consistent finding.

Eosinophilia.—On differential smear, eosinophils were conspicuously absent.

Familial History.—One father was found to be a hay-fever sufferer. In two other cases, allergic stigmata were uncovered in mild form in separated relatives.

Cough.—A persistent and prolonged cough was a consistent complaint. It was often refractive to treatment and quite likely to be a most troublesome phase of the illness.

Epidemic.—There was a previous conviction that these cases occurred in epidemic form. This view that these children were infected with a "wheezing bug" was also shared by other pediatricians in the area. In retrospect, however, this assumption could not be substantiated. Most cases had their onset during the winter months. Ranges from October to March accounted for 80 per cent of the cases, with the heaviest concentrations in December and February. May and July each accounted for one case, and two had their onset in June.

Age.—These patients ranged from three to twenty-six months in age. However, only four cases were over a year of age at the time of diagnosis, and the average age of the entire group was nine months. Six of the children were girls.

X-Ray.—Chest x-rays were taken on twelve of these patients. In three of the cases the radiologist reported the lung fields to be clear. Consistent interpretation of other films reported moderate to marked increase in bronchovascular markings.

Bacteriology.—Nose and throat cultures taken on all hospital patients showed only the usual bacterial flora; staphylococcus, streptococcus and catarrhalis predominating. In none of these cases was *H. pertussis, H. parapertussis* or *H. influenzae* isolated.

FOLLOW-UP

These children have been followed for as long as seven years, although most cases would be nearer the average of about five years. In that interval of follow-up study the following picture has developed.

Eight children, or 40 per cent, of the original number have since developed asthma. All but two of these are now being treated by desensitization, and two are rather refractive cases. Five additional patients, from a

pediatric allergy standpoint, we would diagnose as mildly allergic because of upper respiratory tract infections and wheezing, in one instance requiring epinephrine. However, we cannot classify these as such since this study is but a segment of a comprehensive one in which no interpretation of initial recorded diagnosis has been made.

Skin manifestations have since appeared in three children. One child has eczema while another developed a rather severe drug sensitivity. The third was later diagnosed as having a contact dermatitis.

In two cases other siblings developed urticaria, asthma, or hay fever, although the child in question appears to be well at the present time.

In only two cases have the children or their brothers or sisters failed to show any allergic stigma up to this time.

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306 South Gregson

WASHINGTON STATE SOCIETY OF ALLERGY

On May 21, 1955, the Washington State Society of Allergy was formally organized and by-laws adopted at a meeting in Seattle attended by twenty-six physicians practicing allergy or applying allergy to their practices in the state of Washington.

The following officers were elected:

President.....Lester W. Mittelstaedt, M.D., Seattle, Wash.
Vice President.....Robert A. Stier, M.D., Spokane, Wash.
Secretary-Treasurer.....Lois Frayser, M.D., Seattle, Wash.
Council .....Howard L. Hull, M.D., Yakima, Wash.
J. E. Stroh, M.D., Seattle, Wash.
Leslie E. Hildebrand, M.D., Wenatchee, Wash.
A. R. Altose, M.D., Seattle, Wash.

The next meeting of the Society will be held in Seattle in September, 1955, at the time of the meeting of the Washington State Medical Association. It is the plan of the Society to present scientific programs and to further the standards of the practice of allergy.

RADIOACTIVE IODINE IN THE MANAGEMENT OF PATIENTS WITH SEVERE PULMONARY EMPHYSEMA

ALLAN HURST, M.D., F.A.C.A., MORRIS H. LEVINE, M.D. and D. RUSSELL RICH, M.D.

Denver, Colorado

THE GROWING awareness of the frequency of pulmonary insufficiency in our aging population is demonstrated by the long list of publications on the subject in recent years. Altschule,[1] in his book entitled, *Physiology in Diseases of the Heart and Lungs,* has collected all of the important literature up to the time of the publication of his book in 1954 and notes that "in almost all instances the patients with obstructive emphysema who have been studied developed emphysema secondary to asthma."

The relationship of asthma to the development of emphysema, both in young children as well as in adults and in our aging population, has focused attention on asthma as an important causative mechanism in this regard. The advancing age of our population and decreasing mortality in pulmonary infections have further focused attention on the increasing problem of pulmonary emphysema. One still finds that the only stress laid on the management of the older patient with asthma, chronic bronchitis and emphysema is that of testing and hyposensitization treatment rather than on the problems of the altered physiology and mechanics of breathing that one finds in such cases. At best, the treatment of chronic pulmonary insufficiency has been disappointing and in most instances of only temporary value. Even where the patient appears much improved, a superimposed respiratory infection has been sufficient to upset the delicate cardiorespiratory balance with resultant pulmonocardiac failure.

A review of the important investigations bearing on the physiology and management of pulmonary emphysema has been expertly presented by Segal and Dulfano[8] in their book, *Chronic Pulmonary Emphysema—Physiopathology and Treatment.* More recently the additional publication by Drinker[6] entitled, *The Clinical Physiology of the Lungs,* and the small but beautiful volume by Comroe and his associates[5] entitled, *The Lung,* have almost completed the background data necessary for the understanding of the management and treatment of pulmonary insufficiency.

After applying all of the recommended therapeutic measures in the management of pulmonary emphysema, a large group of intractable cases still remains. In this group of cases the disability is so severe that even

From the General Rose and St. Anthony Hospitals, the Ex-Patients' Sanatorium for Tuberculosis and Chronic Disease, and the University of Colorado School of Medicine.

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slight activities, such as walking from bed to toilet, eating, or mere combing of the hair, may become major efforts. Symptoms such as increased cyanosis, dyspnea, and tachycardia ensue. It is in this group of cases that additions to our therapeutic armamentarium are needed. In addition, as new techniques in treatment are added, new problems such as respiratory acidosis present themselves and it becomes necessary to review fundamental chemistry and physiology to prevent and to treat this serious complication.

In several papers, Blumgart[3] and his co-workers reported beneficial results in angina pectoris and congestive heart failure by production of a hypothyroid state. This was originally accomplished by surgical thyroidectomy, and more recently by radiation thyroidectomy through the use of radioactive iodine (I-131). The rationale is approximately as follows: lowering of the basal metabolic oxygen needs makes available a relatively larger amount of tissue oxygen for other purposes than the basal state. This becomes especially important where a severely restricted amount of tissue oxygen is present. In approximately two-thirds of the cases thus treated there has resulted a substantially greater activity by the patient before distressing symptoms appear.

Stimulated by the work of Blumgart, consideration was given to the possible beneficial results of using I-131 in the parallel problem presented by intractable pulmonary emphysema. Here, too, the tissue oxygen needs are restricted by increased residual air and lowered arterial oxygen saturation. The loss of pulmonary reserve in pulmonary emphysema presents a clinical picture paralleling the loss of cardiac reserve in congestive failure. Lowering the basal metabolic level therefore appears to be as logical in pulmonary disease as in cardiac disease.

It is probable that cor pulmonale is present in some degree in all cases of severe pulmonary emphysema. It appears logical to treat such cases with I-131 in order to diminish the stress on the right heart and pulmonary vascular bed before severe secondary cardiac disease develops. The added procedure, as in Blumgart's therapy of heart disease, would require that the patient be maintained on established methods of therapy as well.

With these thoughts in mind we treated our first case of severe pulmonary emphysema in June, 1953, and since then have treated a total of twenty-eight cases up to April, 1955. Of these twenty-eight cases, only twenty-four have been followed for a sufficient period of time to draw any conclusions.

All patients were hospitalized at General Rose Memorial Hospital and St. Anthony Hospital and many were then sent to the Ex-Patients' Sanatorium for Tuberculosis and Chronic Disease, for further observation. Of the twenty-four cases reported here, there were twenty-two men and two women. Ages ranged from forty-four years to seventy-one years. Twelve men had histories of soft coal mining for many years; the remainder had been in various business occupations including sedentary office

work. In addition to routine physical examinations, histories, fluoroscopic examination of the chest and chest x-rays, blood studies for protein bound iodine as well as I-131 tracer studies were done both before and after treatment as well as cholesterol and cholesterol esters. All patients were studied by electrocardiogram and sixteen of the twenty-four patients showed findings which have been shown to be consistent with cor pulmonale. Seventeen patients of the twenty-four had had a history of at least one bout of congestive failure and at least half of this group were in active congestive failure with enlarged livers and pitting ankle edema at the time of therapy.

Nine of the cases were studied in the Cardiopulmonary Laboratory of the University of Colorado Medical Center. Maximum Breathing Capacity ranged from 14 L to 30 L in eight cases (15 per cent to 36 per cent of predicted values), while the ninth case was 42 L (46 per cent of predicted). The timed vital capacity showed an output in three seconds of 35 per cent to 63 per cent, with the ninth case 98 per cent. Residual air volumes ranged from 50 per cent to 80 per cent in eight cases, while the remaining case mentioned above was 57 per cent, indicating a severe emphysema in spite of the normal timed vital capacity.

The majority of the twenty-four patients had been treated with bronchodilator drugs by mouth, nebulizer and by intermittent positive pressure breathing machines, with only temporary benefit. In several instances pneumoperitoneum was given with symptomatic benefit for a few months. In other cases this form of treatment was initiated but could not be continued because of the excessive abdominal pain. Breathing exercises, corticotropin and cortisone, phlebotomies for hypervolemia as well as restriction of sodium in the diet, the use of various digitalis preparations as well as the mercurials by injection and by mouth had all been applied. In some cases the patients were in such severe congestive failure on admission, that no more than the treatment of this process could be started before I-131 was given. These last cases fell into the category of Group IV of Baldwin and her associates[2] and would be considered as the most severe of all of the pulmonocardiac failure cases.

In a previous publication,[7] we reported on our first twelve cases and noted that except for the first two, 200 mg of propylthiouracil had been given daily for one week to ten days and discontinued forty-eight hours before the blocking dose of I-131. In these initial twelve cases the dose of I-131 ranged from 40 to 50 millicuries in the majority of cases although three patients had to receive an additional 28 to 40 millicuries before an effect could be secured. The symptoms of radiation thyroiditis were severe in several instances and required medication extending from cold compresses and coal tar products up to and including narcotics and cortisone.

In an attempt to diminish this sometimes serious complication by giving divided doses, it was decided that the next group of cases should be

treated in a slightly different fashion. Following the initial diagnostic study, a dose of 20 millicuries of radioactive iodine was given to each patient, followed in two months by another tracer study and an additional 20 millicuries of radioactive iodine. In this later group no instances of radiation thyroiditis have been found. Here no propylthiouracil was given before the first dose, but 200 mg was given daily for one week prior to the second dose because of the theoretically diminished uptake of I-131 by the partially blocked thyroid.

Blumgart has noted in the I-131 treatment of congestive heart failure, that all other current measures must be used simultaneously. The same thought must apply in the treatment of pulmonary insufficiency. It is therefore difficult to exclude the value of the other methods in the total management of any individual case. In addition, improvement must be evaluated in terms of the severity of the condition. Thus a patient in severe congestive pulmonocardiac failure, who becomes compensated and has a more prolonged and comfortable life, may be said to have had at least a fair result. At the other extreme, a cachectic dyspnoeic male who gains thirty pounds and can walk a considerable distance without difficulty may be said to have had a good to excellent result. The semantics here may be difficult but we believe that the point has been made clear.

The improvement noted has been gain in appetite, gain in weight, a sense of well-being, and an increase in exercise tolerance. The anxiety associated with the sensation of smothering, noted in so many severe cases of emphysema, is diminished in our completed cases. In some instances there have developed various degrees of hypothyroidism sometimes requiring small doses of thyroid substance for optimum comfort.

Of the twenty-four cases, two had excellent results, one of whom had been in severe congestive failure while the other was cited above. Eight cases had good results although there were two later deaths, one by accident and another by suicide. Nine cases had fair results while the remaining five cases died early in the course of treatment in congestive failure. It should be noted that there were no poor results as such, except for the deaths in the last five cases. The selection of such severely sick patients can only be excused on the basis of "last resort."

Further study will still be necessary for proper selection of patient, dosage, as well as exact mechanisms involved in the physiologic changes in cardiac output, pulmonary artery pressures, et cetera. Ideally, we should treat cases before severe congestive failure supervenes with the inevitable termination.

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SIXTH INTERNATIONAL CONGRESS OF OTOLARYNGOLOGY

The Sixth International Congress of Otolaryngology will be held in Washington, D. C., May 5 to 10, 1957. The subjects selected for the three plenary sessions are: Chronic Suppuration of the Temporal Bone, Collagen Disorders of the Respiratory Tract, and Papilloma of the Larynx. Outstanding internationally recognized authorities will open the discussion of each of these subjects.

Two types of communications are invited: Contributions to the discussions of the selected subjects, limited to five minutes, and original papers, limited to fifteen minutes. These should be in one of the four official languages of the congress: English, French, German, and Spanish.

Further information regarding this meeting may be obtained from the General Secretary, Paul H. Holinger, M.D., 700 North Michigan Avenue, Chicago 11, Illinois.

AMERICAN MEDICAL WRITERS' ASSOCIATION TO HOLD TWELFTH ANNUAL MEETING

The twelfth annual meeting of the American Medical Writers Association will be held on Friday and Saturday, September 30 and October 1, at the Hotel Jefferson in St. Louis, Missouri. An hour on Friday morning will be devoted to a panel on AMWA services, followed by an address on "Clarity in Medical Writing" by Dr. Joseph Garland of Boston, Editor of the *New England Journal of Medicine,* and a paper on "Do Statistics Clarify or Confuse?" by Alan E. Treloar, Professor of Biostatistics, University of Minnesota. A panel on "Preparation of Medical Presentations" (articles, books, public relations material, motion picture scripts) will comprise the afternoon's program, and the evening will be given over to the annual banquet. Beginning at 8:00 a.m. on Saturday, October 1, a workshop will be conducted by journalism instructors from the Universities of Illinois, Missouri, and Oklahoma, including a give-and-take demonstration on three subjects: First Draft to Printed Article, Specific Devices for Increasing Readership of Medical Articles, and Writing Magazine Articles for the Lay Reader. More information about this interesting program can be obtained from the Association's headquarters at 209-224 W.C.U. Building, Quincy, Illinois.

COMMON HAND ECZEMAS

SAMUEL M. BLUEFARB, M.D.
Chicago, Illinois

IN A recent monograph "The Eczemas,"[5] it is stated that "Eczema of the hands has confronted the dermatologist with some of his most perplexing problems." In my opinion this is an understatement, since eczema of the hands accounts for a significant percentage of partial and total disability among persons having cutaneous disease.

The etiology of hand eczema, as in other eczemas, is multiple and varied. Stokes coined the expressive phrase "multiple factorial etiologic concept" and mentioned such causative factors as heredity, icthyotic, seborrheic, pyogenic, bacterial, psychic, neurogenic allergic metabolic, and the factor of focal infection. It is quite likely that most of these eruptions of the hands are attributable not to a single factor but to several primary and predisposing factors.

The etiology as well as the morphology is variable in most cases. This eczema, or dermatitis of the hands, consists of a vesicular or scaling, oozing or weeping, crusted or infected eruption. In the acute phase, it is characterized primarily by vesicles and erythema; in the chronic phase by thickening or lichenification and scaling. Pruritus may be present in each phase and secondary infection may alter the clinical picture.[6]

Nevertheless, we have attempted to classify all cases of hand eczema seen in private practice during the past ten years, both etiologically and morphologically. It was found that, with certain reservations, 95 per cent of all cases could be included in one of five cutaneous entities (Table I). These five dermatoses are: (1) contact dermatitis, (2) eczematoid ringworm, (3) sweat retention syndrome (dyshidrosis), (4) atopic dermatitis, and (5) nummular eczema.

CONTACT DERMATITIS

Contact dermatitis, or contact eczema, is the most frequent dermatosis affecting the hands. These particular areas are subjected to more external irritants than any other part of the body. The causative agent of contact dermatitis may either act as a primary irritant, thus producing a dermatitis, or it may act as a sensitizer, thereby upsetting the skin equilibrium so that eczema is produced by other chemical or physical agents.

It is not possible to enumerate all the known skin irritants in a discussion of this type, since so many known factors may cause hand eczema. Baer and Ludwig[1] list the most common causes of allergic contact dermatitis as: therapeutic agents used in topical therapy, metals, plants, certain fruits and

From the Department of Dermatology, Northwestern University Medical School, Chicago, Ill.

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TABLE I. CLASSIFICATION OF THE HAND ECZEMAS

	Dermatitis Venenata (Contact Dermatitis)	Eczematoid Ringworm	Nummular Eczema	Atopic Eczema	Sweat Retention Syndrome (Dysidrosis)
Location	Dorsal	Palms	Dorsal	Dorsal	Palms
Sites and Other Distributions	Bilateral—often worse on one hand. Exposed parts	Bilateral—symmetrical. Feet, crurals, "Ids"	Unilateral or asymmetrical if bilateral. Extensors of forearms, anterior aspects of legs and dorsa of feet.	Bilateral—symmetrical. Flexural surfaces	Bilateral—symmetrical. Lateral aspects of fingers, palms and soles.
Primary Lesion	Erythema to bulla depending on irritant	Vesicle or bulla	Papule, vesicle or pustule	Vesicle (microscopic)	Vesicle
Depth of primary lesion	Usually superficial	Very deep	Superficial	Superficial	Deep
Coalescence of primary lesions	Ready coalescence to form diffuse patches	Patch formation, but primary lesions tend to retain individuality	Patch formation, but primary lesions tend to retain individuality	Ready coalescence to form diffuse patches	Lesions retain individuality—often grouped
Margins	Usually poorly defined or sharp in places	Very sharp definition	Sharp definition	Poorly defined—patches shade off into surrounding skin	Sharp definition
Degree of inflammatory reaction	Intense	Variable	Usually moderate	Intense	Very slight
Symptoms	Intense itching	Moderate to severe itching	Little to moderate itching	Intense itching	Intense itching and burning at onset, later mild itching
Season	—	More often in summer	More often in winter	More often in winter	Spring and summer
Response to treatment	Good if source is discovered	Clears often, prone to recur	Clears often, prone to recur	Variable	Spontaneous involution, but recurrence common
Laboratory	Patch tests	Fungus present—but not in "Id" lesion	—	—	—

vegetables, paints, polishes and cleansers, wooden handles of household utensils, plastics, cloth, leather and rubber, cigaret holders cosmetics, telephone receivers, electric razors, chalks, crayons, pencils, fountain pens, and contact allergens encountered in occupations and industries.

ECZEMATOID RINGWORM

In this study eczematoid ringworm is meant to designate an eczematous secondary fungus infection affecting the feet, groin or other areas and is probably produced by allergic reactions, as a result of repeated hematogenous transport of either the fungi and/or their products to the hands resulting in eczematoid ringworm.

A diagnosis of this condition is dependent on the demonstration of a primary fungus infection of the feet or of other areas, with the hand eruption following the activation or irritation of the primary focus. The

hand eruption is usually bilateral and symmetrical and occurs predominantly on the palms and sides of the fingers. The trichophytin test is positive and subsidence of the eruption occurs within a reasonable period after control of the primary fungus infection.

SWEAT RETENTION SYNDROME

The possibility of a sweat mechanism disturbance is not a new concept in the etiology of hand eczema. The older dermatologists spoke glibly of "dyshidrosis" and "cheriopompholyx," but more recently, through the works of Hermann and Sulzberger[4] and others, recognition of the sweat retention syndrome has added considerable knowledge to the pathogenesis of hand eczema. Histologic study of sweat retention reaction would indicate that this condition is not a specific disease but rather a pathologic concept, i.e., plugging of the sweat ducts. The active process of vesicle formation may be produced by any factor which stimulates sweating, such as heat, emotional reactions, cholinergic drugs, ingestion of foods and, possibly, by other factors.

Typical sweat retention syndrome is characterized by deep-seated vesicles which usually appear in groups along the sides of the fingers or on the palms. These lesions occur symmetrically, without previous erythema. There is frequently intense pruritus, six to twelve hours prior to the formation of vesicles, although this symptom may abate after the sudden appearance of the vesicles. The deep-seated vesicles do not tend to rupture, but undergo involution as a result of shrinkage and desiccation. Some vesicles may enlarge to become bullae and occasionally they become pustules.[2] Therapy consists of the usual topical agents, as well as the use of anticholinergic drugs such as Banthine® and Prantal® three to four times daily.

ATOPIC DERMATITIS

Occasionally atopic dermatitis may be localized to the hands. This eruption is patchy, erythematous, thickened, highly pruritic, excoriated and, occasionally, oozing and crusted but having only minor papulovesicular features.[7] The most frequent sites of involvement are the dorsa of the hands and fingers. Familial and personal history of atopic disease may or may not be elicited.

NUMMULAR ECZEMA

Nummular eczema is a localized, patchy type of erythematous lesion occurring chiefly on the hands and upper extremities. It is characterized by small, poorly-defined erythematous and vesicular patches which develop rapidly and are associated with pruritus and exudation.

I am in agreement with Gross et al[3] who state that housewife's eczema is really nummular eczema, precipitated by the chemical action of soap and alkalis. Sulzberger and Baer[8] state that most cases begin "with mild

dryness, redness and scaling, which as the condition becomes more severe under continued exposure to soap and water, leads to fissuring and crusting and eventually to vesiculation and ultimately to thickening and lichenification." This condition frequently involves the left fourth finger under the rings.

There appears to be an increase in housewife's eczema among private patients, particularly during the winter months. Without a doubt this increase is associated with the advent of modern detergents. It may be accepted as a fundamental fact that the more efficient the detergent, the greater the keratin or fat solvent action on the skin. It appears that in order to obtain a superior cleansing agent, the manufacturers have produced not only a cleansing product but also one which acts as a fat solvent to the skin. The skin tends to become harsh and fissured. As a result, there is an increase of dry eczematous reactions on the fingers, wrists or dorsal areas of the hands, with inflammation of the interdigital areas and paronychia.

The constant immersion of the hands in water, even without irritative agents, tends to produce deleterious and macerative changes. The tissues become less resistant to hitherto innocuous chemicals. If, in addition, a fat solvent, such as the detergents, is used on an already dry skin, the soil is ready for the development of typical housewife's eczema.

The management of these patients is tedious, painstaking and, at best, palliative. However, they may be greatly benefitted by a few simple measures, the first of which is reduction of the irritation. They should be instructed to wear cotton-lined rubber gloves or cotton gloves under rubber gloves for periods of not more than fifteen minutes. Since heat will penetrate these coverings, the use of hot water is contraindicated. Dishwashing should be done by soaking the dishes in hot soapy water for thirty minutes, thereby emulsifying the debris, and at the end of this period the water will be sufficiently cool for washing with cotton-lined rubber gloves. For bathing infants, a pair of cotton gloves are worn over the cotton-lined rubber gloves to prevent slipping. Diapers should first be rinsed in clear water to remove the ammoniacal urine. Since fruit juices, fruit, vegetables and raw meats are frequently irritating, the use of canned or frozen products is recommended. These patients should avoid contact with wool, such as in knitting or making of beds. Since ordinary hand cleansing methods are not advisable, a tepid boric acid solution may be used for cleansing. If cotton gloves are worn at all times the hands will require little cleaning, and the patient will not tend to cleanse the hands as frequently.

Another important factor is the reduction of emotional excitement. Although this factor does not cause housewife's eczema, it will certainly aggravate an existing dermatosis. Thorazine,® in doses of 10 mg following lunch and dinner, is useful in alleviating this factor.

For topical application, 1 per cent hydrocortisone in an acid mantle cream

(Cortdome®) or 0.1 per cent Florinef ointment(Squibb), used during the day and a 2 per cent icthyol ointment for night use, are excellent remedies. The results obtained from the use of the silicones has been disappointing. An inflamed skin does not tolerate silicones and these agents do not protect a normal skin from synthetic detergents.

In chronic cases, the judicious use of roentgen therapy gives good results. It should be borne in mind that many of these patients are compensation cases, who do not wish to recover, and, in the case of the housewife, many prefer not to do household tasks.

SUMMARY

In our study of private patients, 95 per cent of the cases of hand eczema can be classified, etiologically and morphologically, into five dermatoses: contact dermatitis, eczematoid ringworm, sweat-retention syndrome, atopic dermatitis and nummular eczema.

Housewife's eczema, a variant of nummular eczema, has markedly increased since the common use of detergents, especially during the winter months. The management of this condition is discussed briefly.

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In the printing of the roster of The American College of Allergists, the name of Dr. Paul Kallós, Sundstorget 5, Helsingborg, Sweden, was inadvertently omitted from the list of Honorary Fellows.

ECZEMA HERPETICUM (KAPOSI'S VARICELLIFORM ERUPTION)

FRED F. FELDMAN, M.D., and BEN A. NEWMAN, M.D.
Beverly Hills, California

IT IS the purpose of this paper to present the basically uniform clinical picture we observed in eight consecutive cases of Kaposi's varicelliform eruption, and to report on recurrences in three of these cases. Etiology, terminology and treatment will also be briefly discussed.

The occurrence of this disease almost exclusively in atopic individuals, and the frequent improvement of underlying eczema following an attack of Kaposi's varicelliform eruption is generaly recognized but remains unexplained.

DESCRIPTION OF CASES

A characteristic and uniform clinical picture was observed in eight cases of Kaposi's varicelliform eruption despite variations in the severity of the disease. The dermatosis we observed was essentially an extensive disseminated herpes simplex infection complicating eczema. The onset was abrupt. The early form of the eruption consisted of erythema, edema, and tense vesicles, both grouped (herpetiform) and disseminated, superimposed on eczema. In a few patients some of the vesicles were umbilicated. All of the patients had long-standing, typical atopic eczema, except for a two-and-one-half-year-old child who was said to have had a recurrent eczematoid dermatitis in the past. The viral eruption in all our patients was confined to the upper half of the body. The face and neck was most commonly affected. Except for the two-and-one-half-year-old child, our patients ranged in age between fifteen and twenty-eight years. In three patients herpes labialis preceded the eruption.

Moderate to severe and, at times, painful regional lymphadenopathy was a characteristic finding in all. Fresh vesicles were usually observed within the first four days of the eruption. New lesions were not seen one week after the onset. Involution of vesicles occurred by desiccation and crust formation.

During the second week of the dermatosis, regression of lymphadenopathy and subsidence of erythema and edema was observed. In most instances a marked improvement of the underlying eczema resulted. The latter observation has been mentioned by others.[7] Fever and symptoms of toxicity occurred in all but two patients. The duration of the disease varied from nine to fifteen days. Mild to severe cases were observed, ranging from one who had an afebrile course of nine days' duration to another whose symptoms of toxicity were alarming. There were no

From the Departments of Dermatology, Cedars of Lebanon Hospital and Los Angeles County General Hosptal.

instances of death. The only complication we observed was photophobia and conjunctivitis which developed in one patient at the height of his eruption.

RECURRENCES

Although recurrent herpes simplex is very common, subsequent attacks of Kaposi's varicelliform eruption are rare.[8] This statement is borne out by the fact that only four reports of recurrences of the disease could be found in the literature.[6,11,18,19]

CASE REPORTS

Case 1—M. C., a seventeen-year-old white girl who has had atopic dermatitis since infancy, developed Kaposi's varicelliform eruption on January 14, 1953. A gradually rising fever reached its height (104°) on January 19. She received a total of 6 gm of Aureomycin® by mouth. The complete course of the infection lasted twelve days.

On February 24, 1953, approximately one month later, there was a recurrence of grouped and disseminated vesicles on an erythematous, edematous base involving the sides of the face and neck. Regional lymph nodes were again involved. On February 26, oral Aureomycin (250 mg every four hours) was started. There was complete subsidence of the eruption by March 2.

On July 1, 1953, the patient noted a few blisters below the right eyelid. Within a few days a disseminated and extensive vesicular eruption involved the right side of the face and neck and the right ear. There was marked regional lymphadenopathy. Aureomycin was administered, and the eruption cleared within a week.

A brief report of two additional recurrent cases follows.

Case 2.—J. B., a nineteen-year-old white boy, has had life-long atopic eczema. On January 10, 1953, he developed herpes simplex of the upper lip which was followed by typical Kaposi's varicelliform eruption two days later. The dermatosis was of ten days' duration. Aureomycin was administered.

On April 11, 1953, approximately four months later, numerous vesicles, erythema and edema, appeared on his left upper and lower eyelids. The eruption extended to the left side of the forehead. The left preauricular and left submaxillary lymph nodes were enlarged. Aureomycin was given, and there was rapid subsidence of the eruption.

Case 3.—R. S., a fifteen-year-old, white boy, has had atopic eczema since infancy. On December 1, 1952, he developed a severe attack of Kaposi's varicelliform eruption which lasted ten days. On February 27, 1953, approximately two and one-half months later, he developed grouped and disseminated vesicles on each upper extremity. There was marked lymphadenopathy of the axillae. This attack subsided by March 2, 1953. He received a total of 4 gm of Aureomycin orally for the recurrent attack.

COMMENT

The course of the recurrent cases reported above confirms the statement by Buerk and Blank[9] that the onset of the recurrent eruption is the same as the primary infection, but that its course is milder and of shorter duration. Our recurrent cases were morphologically similar to the initial

attack but much less severe, yet more extensive than an ordinary confined herpes simplex infection. Kaposi's varicelliform eruption is no more than a disseminated herpes simplex infection complicating eczema. It may vary from a mild recurrent attack (as reported in Case 2), to severe, alarming clinical pictures which may terminate fatally. Kaposi's varicelliform eruption can occur as either a primary infection in a patient with no herpes simplex antibodies at the onset or as a recurrent infection in patients with a high titer of antibodies.[9] The height of the antibody titer apparently determines whether the patient will have an ordinary herpes simplex infection or the more extensive, disseminated form which we term Kaposi's varicelliform eruption (eczema herpeticum). Lynch and Steves[16] have pointed out that minimal to extensive eruptions may occur even in the primary infection.

ETIOLOGY

Kaposi[15] believed that the eruption he described was caused by a fungus. Subsequently, early investigators isolated staphylococci and streptococci from lesions with such frequency that the disease was erroneously considered to be of bacterial origin. In the past, the cause of this disorder has been confused because both the vaccinia virus[10,11,24] and the herpes simplex virus have been recovered from cases called Kaposi's varicelliform eruption. However, the herpes simplex virus has been recovered in the majority of instances,[3,5,6,11,14,16,19,21,23] and in recent years most investigators feel that the latter virus is the actual cause of the disease.

TERMINOLOGY

In 1887 Kaposi called the disease he described "eczema herpetiforme."[15] Unfortunately, subsequent reports were entitled "Kaposi's varicelliform eruption," which became universally accepted through common usage. Kaposi's original title was descriptively accurate. However, as a result of modern acceptance of the herpes simplex virus as the causative agent, "herpeticum" could be more correctly substituted for "herpetiforme." We feel that the title "eczema herpeticum," originally suggested by Lynch,[16] is the best one that has been proposed. Rivers has adopted the latter title in his textbook on "Viral and Rickettsial Infections of Man."[20] In short, with only two words we have a designation which embraces both the clinical picture and the causal agent, and also closely approximates Kaposi's original name for the entity. The term "eczema vaccinatum," its counterpart, can then be applied to the simulating eruption when the cause is found to be the vaccinia virus.

TREATMENT

In the past no treatment for Kaposi's varicelliform eruption was considered effective. Following the introduction of Aureomycin, several papers appeared in the literature which suggested that this drug favorably influ-

enced this disease.[1,4,7,12,13,17] However, contrary reports have also been published.[2,9,22] Baldridge and Blank[2] found that Aureomycin had no *in vitro* or *in vivo* effect against the herpes simplex virus. Buerk and Blank[9] stated that Aureomycin had no specific effect against any virus except the unusually large virus of the psittacosis-lymphogranuloma group.

All of our patients were treated with Aureomycin by mouth. It was our impression that Aureomycin hastened the involution of the eruption and lymphadenopathy in some of our cases. The apparent favorable effect of this antibiotic may be a result of its control of secondary bacterial invaders. Whether secondary invaders play some role in the spread of the infection is not known.[8] However, in spite of the apparent beneficial response from Aureomycin in some of our cases, the clinical picture was not appreciably altered. Evaluation of therapy is obviously difficult because of variations in the severity of this dermatosis. Since recurrent attacks of Kaposi's varicelliform eruption are known to be milder and of shorter duration than the original attack,[9] an antibiotic might be incorrectly considered responsible for an apparent favorable influence.

SUMMARY

Eight cases of Kaposi's varicelliform eruption are reported. Three patients had recurrences. The clinical picture described is essentially an extensive disseminated herpes simplex infection superimposed on eczema. The term, "eczema herpeticum," is suggested as a more appropriate title than "Kaposi's varicelliform eruption" for the true case due to the herpes simplex virus. The accepted designation "eczema vaccinatum" can be reserved for the simulating eruption due to the vaccinia virus. An apparent beneficial effect from Aureomycin was noted in some of our cases. However, the latter impression is guarded in view of variations in severity that may occur in this self-limited disease.

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ALLERGIC VASCULITIS

FREDERICK J. SZYMANSKI, M.D.
Chicago, Illinois

A MORPHOLOGIC pattern characterized by eosinophilic leukocytes invading, and by fibrinoid necrosis destroying, the walls of blood vessels is a type of vasculitis recognized as periarteritis nodosa since 1886. Sulzberger[11] has aptly stated that no tissue alterations are in themselves pathognomonic of allergy. This premise is still correct, but the concept that hypersensitivity may produce necrotizing inflammatory changes in small vessels has been firmly established and is now accepted. This morphologic pattern found in various forms of vascular allergy was originally called periarteritis nodosa, but now is responsible for the terms allergic vasculitis and hypersensitivity angiitis.

Rich[7] has reported a few cases of serum sickness and reactions to sulfonamides in which lesions of periarteritis nodosa were demonstrated microscopically, and later, he and Gregory[8] experimentally produced the typical lesions of periarteritis nodosa in animals. Sterile horse serum was injected into rabbits, and after twelve days skin tests revealed a hypersensitivity to the serum. A few days later one cc of horse serum was injected intravenously, and, after this injection, characteristic systemic lesions of periarteritis nodosa were noticed. From their experiments and clinical experiences they decided that "periarteritis nodosa is a manifestation of anaphylactic hypersensitivity."

Recently, in a survey of periarteritis nodosa,[1] only one-third of the cases displayed signs and symptoms suggestive of sensitivity. This fact, plus additional evidence which will be discussed in this report, has influenced certain investigators to favor the term hypersensitivity angiitis for allergic reactions characterized by the typical necrotizing angiitis, and periarteritis nodosa for the nonallergic alterations. Allergic vasculitis and periarteritis nodosa are now regarded as two distinct diseases, and it is claimed that they can be differentiated clinically and microscopically.[13] Hypersensitivity angiitis is a term favored by some, allergic vasculitis by others, but they can be considered synomymously and used interchangeably.

For the sake of convenience and clarification, widespread disorders associated with a necrotizing vasculitis can be classified into four entities: (1) cutaneous allergic vasculitis; (2) systemic allergic vasculitis; (3) granulomatous allergic vasculitis; and (4) periarteritis nodosa.

It is a well-known fact that the blood vessels of the skin act as the shock tissue in such conditions as urticaria and atopic dermatitis. How-

From the Department of Dermatology and Syphilology, University of Illinois College of Medicine (Service of Marcus R. Caro, M. D.).
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TABLE I.

Types of Extensive Necrotizing Vasculitis	Organs and Tissues Involved	Eosinophilia	Types of Vessels Affected	Course of Disease	General Remarks
Cutaneous Allergic Vasculitis (Allergic arteriolitis)	Limited to the skin	Common	Arterioles, Venules & Capillaries of superficial corium	Mild	Not mentioned often, but a fairly common condition
Systemic Allergic Vasculitis (Hypersensitivity angiitis)	Widespread involvement. Lung & spleen commonly. Skin usually. Kidneys show peculiar type of necrotizing glomerulonephritis	Rare	Arterioles, Venules & small arteries of the collagen type	Fulminating. Few days to few weeks	Serious and fatal disease
Granulomatous Allergic Vasculitis (Allergic granuloma)	Heart, liver, spleen, kidneys, G-I tract, gall bladder, pancreas, lungs & skin	Common	Small arteries of the collagen type	Varied but not as rapid as above. 3 weeks to 5 years	Extravascular granuloma resembles sarcoid
Periarteritis Nodosa	Heart, Kidney, G-I tract, pancreas. Lungs & spleen not involved	Common	Small and medium-sized arteries of muscular type	Slow but progressive. Month to years	Cortico-steroids may produce therapeutic paradox

ever, these two disorders were not included in our list because they fail to demonstrate necrosis involving arterioles and venules. Toxic erythemas elicited by a sensitivity to drugs and characterized by a perivascular infiltrate of lymphocytes and eosinophils were also excluded because fibrinoid necrosis is lacking.

The four entities mentioned in the classification possess clinical and pathologic features that enable us to distinguish them. Each of these conditions will be described in detail.

CUTANEOUS ALLERGIC VASCULITIS

Of the forms of necrotizing vascultis, this variety is mentioned least of all. Ruiter[9,10] has studied this condition at great length. Originally, he used the term cutaneous allergic vasculitis, which is favored by the present author, but later designated the condition as allergic cutaneous arteriolitis. At one time it was also referred to as the cutaneous form of periarteritis nodosa.

The concept that a necrotizing vasculitis can be limited to the skin exclusively may seem implausible. However, examples of lesions localized in various organs have been studied and reported. Plaut[6] has described necrotizing arteritic lesions limited to the appendix in eighty-eight cases. The presence of lesions resembling periarteritis nodosa located in the pulmonary arteries of individuals with congenital heart disease[5] lends credence to the hypothesis that necrotizing vasculitis can occur solely in the skin.

Cutaneous allergic vasculitis is an ailment which exhibits a benign course, with its lesions restricted to the skin. Sensitivity to a drug is the usual

pathogenic basis for the development of an eruption which is bilateral and symmetrical, suggesting a hematogenous dissemination. The condition occurs mainly on the extremities and takes various forms; however, papules reminiscent of urticaria represent the most typical lesions. Such papules are more persistent than the wheals of urticaria. Pin-point vesicles or small hemorrhagic crusts may be located at the summit of the papules. Every now and then the eruption is macular with central purpuric spots, and cases resembling Schönlein's purpura have been noted. Others have demonstrated cutaneous manifestations suggestive of a papulo-necrotic tuberculid. Systemic signs and symptoms are noticeably absent, except for eosinophilia of the blood.

Microscopically, the smaller blood vessels such as the arterioles, venules, and capillaries in the upper corium are involved. They show a mild degree of fibrinoid necrosis along with inflammation affecting all three layers of the blood vessels. Lymphocytes, eosinophils, and eosinophilic leukocytes are the cells comprising the inflammatory infiltrate. The condition usually subsides before much fibrosis can develop.

As one might suspect from the presence of lesion solely in the skin, the prognosis is good in all individuals with cutaneous allergic vasculitis. Discontinuation of the offending drug usually produces a fairly rapid clearing of the skin.

SYSTEMIC ALLERGIC VASCULITIS

This generalized and fulminating disease, showing necrotizing vasculitis and produced by an antigen-antibody reaction, was assumed at one time to be a form of periarteritis nodosa. However, systemic allergic vasculitis is now considered the proper designation for extensive vascular disorders generated by sensitization mechanisms.

Sensitivity to serums and drugs seems to be the most important etiologic mechanism noted in the cases of systemic allergic vasculitis. Sulfonamides, iodides, penicillin, thiouracil, thiourea and sodium dilantin are some of the drugs able to incite a systemic necrotizing angiitis. Harkavy[2] studied fifteen patients suffering with typical bronchial asthma of whom four were examined at autopsy. Among the eleven that survived, biopsies of cutaneous lesions disclosed the typical vascular pathology found in periarteritis nodosa. Necrotizing arteritis of the lungs, myocardium and other vessels was demonstrated in the four fatal cases. The chief precipitating factor was considered to be a bacterial allergy resulting from chronic sinus infection. Another case is reported[13] of a patient with a long history of bronchial asthma, terminating in death during an attack.

Systemic allergic vasculitis is a fulminating disease with a short duration. The length of the terminal illness extends from a few days to a few weeks, always less than a month. Almost any tissue of the body may be involved, including the skin. Cutaneous manifestations include erythema, urticaria, angioneurotic edema, purpura, and hemorrhagic necrosis. Von

Wyke and Hoffman[12] report a case of fatal exfoliative dermatitis from sodium dilantin sensitization.

Although widespread involvement is observed, there seems to be distinct sites of predilection which distinguishes systemic allergic vasculitis from periarteritis nodosa. Lesions in the pulmonary vessels and in the follicular arteries of the spleen, found in systemic allergic vasculitis, are absent in periarteritis nodosa. An unusual type of necrotizing glomerulonephritis is characteristic of generalized hypersensitivity angiitis, but apparently not of periarteritis nodosa. Myocardial lesions have also been described, but eosinophilia seems to be rare.

Arterioles, venules, and small arteries are affected by this systemic allergic disease, but large arteries of the muscular type are rarely involved. Fully developed lesions consist of localized fibrinoid necrosis destroying a portion of the vessel with a pleomorphic infiltrate surrounding and invading the vessel walls. Eosinophils and eosinophilic leukocytes are usually abundant in tissue sections. No evidence of healing can be found in systemic allergic vasculitis because of the rapid and fulminating character of the disorder.

A rapid diagnosis, based upon a history of drug or serum intake after previous exposure and confirmed by a skin or kidney biopsy, is imperative, inasmuch as cortisone and ACTH may be life-saving.

GRANULOMATOUS ALLERGIC VASCULITIS

This variety of necrotizing vasculitis is a widespread condition exhibiting cutaneous and systemic manifestations. It is often fatal, but the course is slower than in systemic allergic vasculitis. The duration of the terminal illness in the fatal cases varies from three months to five years. Churg and Strauss[1] have studied a group of these cases, and they prefer the term "allergic granulomatosis." All of their cases were associated with asthma. The presence of a granulomatous reaction situated extravascularly is probably the most important feature distinguishing this condition from systemic allergic vasculitis.

In addition to the asthma, the patients exhibit fever, hypereosinophilia, and symptoms of cardiac failure, renal damage, and central nervous system injury. Recurrent bouts of pneumonia are found in nearly every case. Some present the typical clinical and roentgenologic findings of Loeffler's pulmonary infiltrations. Hypertension is frequently reported, and abdominal pain and bloody diarrhea are common complaints, indicative of gastrointestinal involvement.

Skin lesions consist of erythema, maculopapules, pustules and purpura. Deep subcutaneous nodules seem to be the most characteristic lesions. The present author has seen an example of erythema annulare centrifugum produced by an injection of trichophytin antigen intradermally into a patient with acute mycotic infection involving the toes and adjoining webs.

Biopsy of one of the annular skin lesions revealed microscopic changes similar to the allergic granuloma described by Churg and Strauss.

The gross pathologic findings in granulomatous allergic vasculitis consist of nodular swellings along the course of small arteries of many organs as the heart, liver, spleen, kidneys, gastrointestinal tract, gallbladder, pancreas and a few others. The lungs exhibit gross vascular involvement and patchy pneumonic consolidations.

Microscopically the arterial alterations are essentially similar to those usually seen in periarteritis nodosa. The typical segmental fibrinoid necrosis of the vessel wall accompanied by an inflammatory response within and around the vessels with eosinophilic leukocytes predominating, is distinctive and always present. Aneurysms may be produced at times. An additional feature, not seen in other varieties of necrotizing vasculitis, is the extravascular granulomatous nodule located around or near small arteries and small veins. These nodules show a central eosinophilic core surrounded by radially arranged macrophages and giant cells of the foreign body or Langhan's type. The eosinophilic area contains necrotic cells and severely altered collagen fibers. The collagen change can be classified as an example of fibrinoid degeneration. Eventually fibrosis appears with resultant scarring. The histopathologic pattern of granulomatous allergic vasculitis resembles the changes seen in sarcoidosis and erythema induratum, except for the presence of numerous eosinophils and the necrotizing vasculitis in allergic granuloma. Granulomatous allergic vasculitis is a serious disorder, though not as fulminating as systemic allergic vasculitis. Eleven of the thirteen cases studied by Churg and Strauss[1] were dead at the time of their report.

PERIARTERITIS NODOSA

Periarteritis nodosa was the name given to the entire group of widespread disorders exhibiting an inflammatory necrotizing vasculitis, whether allergic or nonallergic. However, more and more evidence is being accumulated enabling us to separate periarteritis nodosa from allergic vasculitis, and clinical, pathologic, and experimental data substantiating this theory are now available.

Two-thirds of the reported cases of periarteritis nodosa fail to exhibit clinical evidence of sensitization. Furthermore, in animals, widespread periarteritis nodosa is produced experimentally by methods completely outside the realm of allergy.[3] Infarction of the rat kidneys is followed within a few days by the development of necrotizing vascular disease in the mesentery, pancreas, stomach, large intestine, kidney and testis. The possibility that a necrotizing substance derived from the kidney was responsible for the development of periarteritis nodosa is suggested, but not proved.

Pathologically, there are differences which enable Zeek and her associates[13] to distinguish periarteritis nodosa from the vascular lesions of hy-

persensitivity. The heart, gastrointestinal tract, and pancreas are affected with greater frequency in periarteritis nodosa, the spleen and lungs more often in allergic vasculitis. Eosinophilia is common in periarteritis nodosa, but rare in systemic allergic vascular diseases. In periarteritis nodosa the pathologic changes occur at the bifurcation of small and medium-sized arteries with muscular elements, usually near the site of entrance into viscera. As stated previously, allergic vasculitis involves capillaries, arterioles, venules and small arteries, while the larger arteries of the muscular type are rarely if ever involved. In periarteritis nodosa, there are lesions in all stages of development, beginning with proliferation of cellular components, then exudation, thereafter necrosis of the vessel wall with inflammation, and finally the formation of aneurysms and fibrosis. In allergic vasculitis all of the lesions appear to be of an equal age and in the same stage of development.

Periarteritis nodosa is usually of long duration, persisting for months or years as a chronic illness with remissions. Systemic manifestations are multiple, dependent on the organs affected and the amount of vascular damage done. Fever, weakness, headaches, and muscular pains are common complaints. Despite the remissions, the course is usually progressive, and the patient eventually succumbs to cardiorenal failure. The signs and symptoms referable to the kidneys are probably the most prominent, and the incidence of hematuria is high. Clinical manifestations suggestive of coronary or hypertensive heart disease may appear, and peripheral neuritis is quite common. Gastrointestinal symptoms, commonly noted in periarteritis nodosa, have not been observed in allergic vasculitis.

The lesions in the skin are also variable in type. Erythematous, vesicular, pustular, and necrotic eruptions have been observed. Subcutaneous nodules, urticaria, and purpura occur with some degree of frequency. An eruption of the livedo racemosa type on the extremities has been noted on a few occasions. A biopsy of most of the cutaneous lesions reveals the typical histopathology, a convenient diagnostic procedure that many physicians seem to ignore. Malkinson and Wells[4] claim that cortisone and corticotropin are the most effective therapeutic agents available at present for the treatment of periarteritis nodosa; however, they warn us that healing consequent to treatment in diseases showing diffuse arterial involvement may be followed by vascular obliteration and multiple infarctions. Renal failure and hypertension may result from such an extensive healing effect.

SUMMARY

1. Allergic vasculitis and periarteritis nodosa are distinct diseases. The latter term should be reserved for systemic diseases of necrotizing vasculitis in which clinical evidence of sensitization is absent.

2. Widespread disorders, whose common denominator is necrotizing vascultis, are classified and discussed.

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55 East Washington St.

PAN AMERICAN MEDICAL ASSOCIATION CONGRESS

The tenth Inter-American Congress of the Pan American Medical Association will be held in Mexico City, March 25-31, 1957. The Congress will be held in sections covering all branches of medicine and surgery. The Association has forty-two medical sections, including the new "Section of General Practice." A large number of physicians are expected to attend from all of the Latin American countries, as well as from the United States and Canada. The president of the Association is Dr. Pedro A. Gutierrez Alfaro, Minister of Sanitation and Public Welfare of Caracas, Venezuela, and the executive director is Dr. Joseph J. Eller, 745 Fifth Avenue, New York, N. Y.

On the Monday and Tuesday of the week following this Congress, medical meetings will be held in Guatamala City in conjunction with the Association's local chapter.

ACUTE ALLERGIC REACTIONS TO COW'S MILK

C. COLLINS-WILLIAMS, M.D., F.A.C.A.
Toronto, Ontario

A GREAT deal has been written about allergy to cow's milk. This subject is becoming more and more important as breast feeding becomes less popular and the feeding of cow's milk in the newborn nursery more popular. In the literature there are reports indicating allergy to cow's milk as the sole or primary cause of the following clinical syndromes in certain patients: eczema, urticaria, angioneurotic edema, Henoch-Schönlein purpura, diaper rash, circumoral pallor, pylorospasm, colic, vomiting, diarrhea, constipation, anorexia, hematemesis, flatus, abdominal pain, refusal of milk, mucus in the stools, melena, celiac syndrome, eructation of gas, ulcerative colitis, regional enteritis, cough, croup, choking, gagging, excess mucus in the throat, chronic nasal discharge, sneezing, nasal itching or rubbing, asthma, fever, frequency, eneuresis, hematuria, general irritability, convulsions, headache, nervous storms, migraine, severe behaviour disturbances, excessive crying, excessive sweating, toxemia, apathy, listlessness, cyanosis, collapse, and fatal and non-fatal anaphylactic shock.

This paper will be limited to a report of one case of acute non-fatal allergic shock to cow's milk and a discussion of the previously reported cases.

CASE REPORT

This infant was born after a noneventful pregnancy and delivery. The mother had consumed approximately six glasses of milk daily during her pregnancy. The infant was breast fed and did not receive any cow's milk at all until two months of age. At this time, because of illness in the mother, the infant received a feeding of evaporated milk formula. He objected very strenuously to being fed the milk, repeatedly thrusting the bottle out of his mouth, but was forced to take approximately two ounces of the formula which would contain about ⅔ of an ounce of evaporated milk, boiled for three minutes. Immediately after this feeding he vomited, had several loose stools and was very pale. During the next eight hours he remained very pale and there were two more episodes of vomiting and four loose stools. Then, the color rapidly returned to normal and the infant seemed well again. Breast feeding was resumed but no particular significance was attached to this episode and no further cow's milk was given in any form until six months of age. At this time he was given some cereal, previously well tolerated for several months, to which was added approximately one teaspoonful of evaporated milk which had been boiled for three minutes. He objected to the feeding and was made to take only part of it. One half hour later there was vomiting, diarrhea and pallor. The symptoms lasted for only one half hour. No further cow's milk was given until two weeks later when the same procedure with the cereal and evaporated milk was repeated. This feeding was resisted very strenuously also, but the infant was forced to take

From the Allergy Clinic, Hospital for Sick Children, Toronto, and the Department of Pediatrics, University of Toronto.
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TABLE I. SUMMARY OF REPORTED CASES OF ALLERGIC REACTIONS TO COW'S MILK

Number of Cases	Physician Reporting	Year of Report	Reference in Literature	Age at Time of Shock	Type of Cow's Milk Producing Shock	Skin Tests to Cow's Milk	Successful Feeding	Fatal (f) or Nonfatal (nf)	Other Allergies	Additional Notes
1	Talbot	1916	19	few months	raw milk	slightly +	goat's milk	nf	Nil	—
1	Blackfan	1920	2	2½ mos.	raw milk	general reaction	goat's milk	nf	Nil	—
1	Park	1920	14	6 wks.	raw milk	negative	goat's milk	nf	Nil	First shock reaction not very severe. Very severe shock followed condensed milk.
1	Carmichael	1920	8	6 mos.	raw milk	negative	goat's milk	nf	—	—
2	Tisdall & Erb	1925	20	6 mos.	raw milk	+cow +goat	oral hypo-sensitization	nf	Nil	—
				10 days	cow's milk protein in breast milk	+cow +goat	breast	nf	Nil	Diagnosis in retrospect when acute symptoms followed cow's milk later on.
1	Cummings	1928	5	8 mos.	raw milk	markedly +	goat's milk	nf	slightly sensitive to egg	—
1	Ashby	1929	1	9 mos.	raw milk	+cow +goat	oral hyposensitization	nf	eczema, asthma, sensitive to a large number of foods	—
1	Richet	1931	17	several months	raw milk	—	—	f	—	milk had previously caused vomiting and diarrhea
2	Kerley	1936	11	5 mos.	—	negative	goat's milk	nf	—	symptoms brought on by few drops of milk
				10 mos.	—	negative	—	f	—	infant had invariably refused milk
5	Hill	1939	9	—	—	negative	human milk	nf	no eczema	—
				—	—	negative	goat's milk	nf	no eczema	—
				—	—	negative	human milk	nf	no eczema	—
				—	—	not done	goat's milk	nf	no eczema	—
				—	—	strongly + cow & goat	sobee	nf	eczema	—
2	Hill	1939	9 personal communication from Smith	—	—	—	goat's milk	—	—	—
				—	—	—	goat's milk	—	—	—
7	Hill	1939	9 personal communication from Kerley	—	—	negative	—	—	—	—
				—	—	negative	goat's milk	—	—	—
				—	—	negative	goat's milk	—	—	—
				—	—	negative	goat's milk	—	—	—
				—	—	negative	goat's milk	—	—	—
				—	—	positive	—	—	—	—
				—	—	positive	—	—	—	—
1	Hill	1939	9 personal communication from Morse	—	—	—	goat's milk	—	—	—
1	McLendon	1943	13	2 mos.	—	—	oral hypo-sensitization	nf	Nil	—
1	Clein	1951	4	—	—	—	—	nf	—	—
1	Burrage et al	1954	3	4 mos.	—	P-K pos. for cow's milk	Nutramigen	nf	Nil	originally diagnosed as adrenal insufficiency
1	Collins-Williams	1955	present paper	2 mos.	evaporated milk	not done	breast milk	nf	Nil	perfectly healthy in every other respect

Total = 30

most of it. One half hour later he vomited and passed a loose stool and went into an acute state of shock with a very feeble pulse. The heart was very rapid and respirations were only three per minute. The color was ashen grey and the infant appeared to be dead. Adrenaline was administered immediately and given on two more occasions during the next hour. After the first initial state of shock which lasted for approximately five minutes there was very slow recovery, the heart becoming slower, the color better, the respirations faster, and one hour after the episode there was not any evidence at all to suggest that anything untoward had happened. The infant's condition then continued to appear perfectly normal. No cow's milk was given for several weeks, breast feeding being continued until he was eleven months of age. At seven and a half months of age it was decided to orally hyposensitize him. This was started by placing one teaspoon of pasteurized skimmed milk in a quart of water, giving one teaspoonful of the dilute mixture and very gradually increasing up to one teaspoonful of pure pasteurized skimmed milk. This was usually given in the cereal. It took a period of about two and one half months to increase the daily consumption to one teaspoonful of undiluted milk. This process was uneventful except that any milk which touched the face resulted in urticaria at the site. This urticaria resulting from contact of milk, lasted until he was one year of age. At the age of two and a half years he can take about four teaspoonfuls of milk on cereal without any untoward reactions. More causes very soft stools but no other symptoms. It is quite possible that he could take more milk without a more serious reaction but for obvious reasons no further attempt has been made to estimate the full extent of his tolerance. During this time calcium supplement has been given. In all other respects, the infant's course has been completely uneventful. He has gained well, weighing 30 pounds at two and a half years.

There are no other manifestations whatsoever of allergy in the child and, furthermore, there is no history of major allergy in either side of the family. The maternal grandmother suffers allergic shock on the ingestion of mushrooms which developed in late adult life. The mother suffers a fixed drug eruption following the ingestion of barbiturates. Otherwise there is no family history of allergy whatsoever.

REVIEW OF THE LITERATURE

The first report on an acute allergic reaction to cow's milk appeared in the German literature in 1905.[6] Subsequent reports[18] have appeared in the foreign literature since that time. Because of the difficulty in evaluating these early cases critically, they are not included in the following discussion. They include several cases of allergic shock, many of which were fatal. Many of these are briefly reviewed in the English translation of the text by Laroche et al.[12] Twenty-nine case reports have appeared in the English language literature, the first in 1916.[1-5,8,9,11,13,14,17,19,20] Twenty-five of these, including cases that were reported for the first time, were summarized briefly by Hill in 1939[9] and these, together with the additional cases and the one reported here, are summarized in Table I.

This table includes as complete information as could be obtained from the case reports. From the information available it is apparent that most of the patients were young infants usually with no other manifestations of allergy. Skin tests with cow's milk were negative as often as they were positive. Goat's milk was very frequently a satisfactory substitute for feeding the infant. Only two of the reactions were recorded as fatal and

presumably the other twenty-eight were non-fatal. The case here reported is the only one in which the infant had received only evaporated milk. In his paper Hill[9] goes into considerable detail about the immunochemistry of cow's milk proteins. Because this is so important in understanding cow's milk sensitivity and because it has received so little attention in the literature on cow's milk sensitivity since that time, it is worth while reviewing it here. Hill points out that it has been definitely established by many investigators that cow and goat casein are immunologically almost identical. The situation for lactalbumin is not so clear. Although it is usually stated in the literature that cow and goat lactalbumin are immunologically distinct, he found original work on this subject reported only by Von Versell,[21] who found that human and cow lactalbumin were entirely species specific, but did not find that cow and goat lactalbumin were sharply and definitely species specific. He showed only that they were not identical and showed a somewhat greater specificity than the corresponding caseins. On the basis of this work and from his own work on milk sensitive eczematous infants, Hill concludes that the milk-sensitive infant may fall into one of four categories: (1) He may be sensitized to the species specific factor of cow lactalbumin alone; (2) he may be sensitized also to the factor common to both cow and goat lactalbumin; (3) in either of these categories there may be sensitization to casein as well; and (4) a much smaller group may be sensitized to casein alone. As Hill points out, goat's milk as a therapeutic agent is indicated only in the first group.

The study of milk-sensitive cases is further complicated by the fact that casein extracts for skin testing are very difficult to obtain in a state free from lactalbumin, so that a positive skin test with casein is not diagnostic for casein sensitivity unless the skin test with lactalbumin is negative or unless it can be shown that a skin test done with the concentration of lactalbumin in the casein testing material would be negative.[10] Hill[9] from a study of the twenty-five cases of acute anaphylactic shock to milk concludes that most of these cases, which usually do not have eczema, are sensitive to the species specific fraction of cow lactalbumin alone. That is, they fall into the group that can tolerate goat's milk. Of the twenty-five cases, fifteen were fed goat's milk without symptoms and in the others it was not tried. Hill concludes further that the immunologic situation in many of these infants seems to be somewhat different from those with eczema. They are not likely to have other sensitivities and they more often give negative than positive skin tests to milk. On the other hand, if an eczematous infant is acutely sensitive to milk, strongly positive skin tests to both cow and goat milk are likely to be present.

Ratner[15] has pointed out that these infants sensitive to milk may become sensitized in several ways. They may be sensitized either actively or passively *in utero*, by the normal passage of milk protein through the intestinal wall, or by the occasional feeding of raw milk during the newborn period,

which can give rise to a state of hypersensitiveness. For the prevention of milk sensitivity he recommends the taking of only moderate amounts of milk during pregnancy and the careful curbing of excessive amounts of raw milk during the latter months of gestation so as to avoid the possibility of inducing congenital sensitization. Isolated feedings of raw cow's milk to breast-fed infants during the newborn period should also be avoided. For treatment of milk-sensitive infants he recommends that all raw milk should be eliminated from the diet, including the milk used in the preparation of foods. Evaporated milk should be used in place of raw milk and the patient gradually orally hyposensitized by the administration of minute amounts of raw milk with continued use of the denatured milk throughout the entire procedure.

DISCUSSION

These cases of allergic reaction to small quantities of cow's milk illustrate how very acutely sensitive an infant can become to a food protein. Although rare in themselves, they suggest that less severe sensitivity reactions to cow's milk are common, a fact which is substantiated by a review of the literature. One must conclude that the infant reported here was actively sensitized *in utero*. It is quite certain that he did not receive any cow's milk in the newborn nursery or at home until two months of age, when he had the severe vomiting and diarrhea following the ingestion of evaporated milk, and no more until the similar reaction at six months and the acute allergic reaction at six and a half months. The only other possible source of cow's milk protein would be via the breast milk. This does not seem plausable as a cause for sensitization, since, if cow's milk protein were present in the breast milk, it should have caused symptoms in such an exquisitely sensitive infant, and breast milk was tolerated very well both before and after the allergic reaction.

Although, as Ratner points out, most milk-sensitive infants can tolerate evaporated milk while they are being orally hyposensitized to raw milk, the case reported here is an obvious exception. The use of goat's milk was not tried because breast milk was available. Another observation about milk allergy is that it tends to affect subsequent children. This has been repeatedly observed by the author in the more common forms of milk allergy, such as diarrhea. Whether this is due to heredity or due to some peculiarity of the mother which facilitates the establishment of *in utero* sensitization to milk in subsequent offspring is not proven one way or the other and will not be discussed here. In the present case there is certainly nothing to support heredity as the cause, whereas the mother's high intake of milk during pregnancy gives some support to the theory of sensitization *in utero*, as has been postulated by Ratner.[16]

From the above observations it would seem that the best way to handle cases of acute sensitivity to cow's milk is as follows:

1. *Attempts to prevent sensitization to cow's milk in the newborn infant.*—(a) The infant should be breast fed from the time of birth. (b) Occasional supplementary feedings of cow's milk should never be given. It should be a rule in all newborn nurseries that, if an infant is to be breast fed, any necessary supplement given before the flow of breast milk is well established should consist only of lactose or glucose water. If it is found necessary to use cow's milk either as a supplementary or sole feeding, this should be given in the form of evaporated milk and once it has been started it should be continued daily. (c) If minor sensitivities to cow's milk do appear, the evaporated milk should be withdrawn from the diet for at least several months and a milk substitute used. After a period of several months evaporated milk can then be tried in small quantities and gradually increased if tolerated.

2. *Treatment once acute sensitization to cow's milk has become manifest.*—(a) The infant should be breast fed if possible, the mother restricting her own milk intake to one or two glasses a day with supplementary calcium. (b) If the infant cannot be breast fed, a milk substitute should be used. Goat's milk may be used in the patients who have suffered allergic shock but had no other manifestations of allergy. (c) Once all symptoms of milk sensitivity have subsided, the infant should be started on an oral hyposensitization program with drop doses of pasteurized milk, which has been boiled for three minutes, increasing gradually as fast as possible without precipitating symptoms.

3. *Attempts to prevent acute milk sensitivity in subsequent offspring.*—(a) Throughout her pregnancy the mothers' intake of raw cow's milk should be restricted to two glasses a day with the addition of added calcium. (b) The infant after birth should be breast fed entirely. If this is impossible, a milk substitute should be used for the first few months of life and cow's milk rigidly avoided in any form as has been repeatedly emphasized by Glaser.[7] (c) Between three and six months of age evaporated cow's milk may be tried, in small quantities at first.

SUMMARY

The literature on sensitivity to cow's milk is briefly reviewed with a detailed review of the reported cases of acute allergic reactions to cow's milk. A new case of such reaction to cow's milk is reported, the thirtieth case to appear in the English language literature. This is the first case to be reported in which the only milk the infant had received prior to shock was evaporated milk. Suggestions for the prevention and treatment of these cases are given.

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1421 Danforth Avenue

MEXICAN SOCIETY OF ALLERGISTS

At a meeting held on April 29, 1955, in León, Gto., the Mexican Society of Allergists elected the following officers to serve for the year 1955-1956: President, Dr. José Luis Cortés, México, D. F.; vice president, Dr. Oscar de la Fuente, Monterrey, N. L.; secretary, Dr. Fernando Martínez, México, D. F.; and treasurer, Dr. J. M. Lopéz Zanabria, León, Gto.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

PASSIVE TRANSFER OF DELAYED CUTANEOUS REACTIVITY TO TUBERCULIN BY A SPECIAL PLASMA PROTEIN FRACTION

There are many responses to believe that the delayed (or tuberculin) type of cutaneous reactivity must be correlated with an antibody present in the circulating body fluids. No such antibody, however, has hitherto been demonstrated. And passive transfer of delayed type reactivity has succeeded only with cellular material. The April issue of the *Journal of Experimental Medicine* contains an article by Cole and Favour (Harvard) which may be an important contribution to the solution of this puzzle.

Before relating the new findings, it may be useful to recall a few important data on tuberculin reactivity elaborated during recent years. Tuberculin contains two biologically active components. One is a polysaccharide which is actively antigenic. It also appears to be the fraction of tuberculin which is absorbed upon the surface of erythrocytes and thus becomes the reagent for the demonstration of circulating antibody in many cases of human tuberculosis (Dubos-Middlebrook). This fraction, however, does not evoke the delayed type of response characterizing the classic tuberculin reaction. This reaction is produced by the other component of tuberculin, which is a protein of low molecular weight, and which has become familiar to the medical profession as one of the common agents of testing for tuberculin sensitivity under the name of PPD (purified protein derivative). Being thus marked as the component against which the allergic reaction of the tuberculous patient is directed, it has nevertheless been the despair of the immunologist because of its low ability of evoking antibody response which would permit its demonstration by any of the classic methods *in vitro* and *in vivo*. Recently, however, Boyden found a reaction using PPD adsorbed on tannic acid treated erythrocytes, by which circulating antibodies can be demonstrated in tuberculosis. And it has been shown that this antibody is, in all likelihood, directed against the tuberculin's protein.

Cole and Favour, working with tuberculin-positive guinea pigs, report that they succeeded in obtaining passive transfer of delayed type reactivity against PPD with a subfraction of alpha globulin, for whose isolation they elaborated a special method. This fraction also contains the reactivity with Boyden's reagent. By contrast, the (anaphylactic) antibody to the poly-

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Progress in Allergy

BRONCHIAL ASTHMA

A Review of the Recent Literature—1954

PHILIP M. GOTTLIEB, M.D., F.A.C.A.
Philadelphia, Pennsylvania

Articles and reports on the subject of bronchial asthma have continued to appear during the past year in a large and apparently never-ending stream. The *Virginia Medical Monthly*[31,68,96,140,141,232,337,338,339] and the *Journal of the Irish Medical Association*[248] have each devoted most of a recent issue to symposiums on the subject.

As might be expected regarding a disease that frequently presents difficult therapeutic problems, a large proportion of the papers appearing in the literature are concerned with treatment. Other aspects receiving considerable attention are classification, pulmonary function and respiratory physiology, and fatalities from asthma. At the same time, diagnosis and consideration of etiologic factors have not been neglected.

It is probably not unfair to state that little in the nature of startlingly new or original approaches has appeared in the past year. On the whole, attention has centered on a better integration and understanding of accepted principles and on the more careful application and evaluation of existing therapeutic methods. As in other fields of medicine, divergent and even contradictory opinions are not uncommon, not alone in the single year, but also when the thinking of several recent years is compared. Bowen[33] has had the courage to criticize and re-appraise many of our current concepts, and it must be admitted that many fall short. The need for intensive investigation of many of the facets of this difficult disease is obvious.

Asthma in cattle is being studied at the Colorado Agricultural Experiment Station.[137] Cow asthma is characterized by labored breathing, loud grunting on expiration, bloating, and failure to eat. It appears in mountain areas and usually in the fall; most cases occur when cattle are brought down from high summer ranges to graze on irrigated meadows. Extreme pulmonary emphysema may ensue. Asthma in cattle is considered to be of unknown cause and unknown treatment, but one may wonder whether the diagnostic and therapeutic approaches employed in human asthma may not be fruitful.

As in so many other realms of scientific observation and discovery, the Russians have claimed scientific priority in establishing the relationship between bronchial asthma and disorders of the central nervous system.[47] Although the reviewer was unable to read this article or have it translated, its title alone expresses the intent.

In general, the present review has followed the pattern of its predecessors.[130,131] It was deemed desirable, however, to add a section on classification and to make some minor changes in the arrangement of the sections on treatment. It was also decided to dispense with the section on Asthma in

Children, since the annual review on pediatric allergy[59] covers the subject, and since, broadly speaking, nearly all that is true of childhood asthma also holds true of adult cases. Accordingly, the various reports dealing exclusively with asthma in the young[45,46,68,163,164,201,371] are considered in the appropriate sections. Swartz's book on the allergic child[333] contains some helpful instructions to the parents of the asthmatic youngster.

As heretofore, the reviewer has not felt entirely confined to reports appearing in the last calendar year, and has included a number of more recent ones, as well as some dating from 1953, but becoming available only since the last review was written.

INCIDENCE AND MORTALITY

Feinberg[92] has performed a welcome service in reminding the profession that there are probably no less than two million persons with asthma in this country, and that several hundred thousand of them are incapacitated. The average well-trained doctor is likely to be a novice in the management of chronic asthma or may subscribe to the old superstition of waiting for a child to outgrow his asthma, with unhappy consequences. Swineford[337] reported that in a five-year period, asthma was diagnosed at the University of Virginia 3,779 times and that no other important diagnosis was recorded as often. In a British general practice comprising about 4,000 patients, Hamilton and Bendkowski[146] saw sixty-eight cases of asthma in a period of one year. Most of them had been suffering from the disease for more than two years, and more than half of them for more than five years. Many also had other allergic diseases, most often allergic rhinitis. Asthma constituted 1.7 per cent of their total practice and 32.5 per cent of the allergic cases.

Reports emanating from England, Germany and Switzerland emphasize the not insignificant mortality rate of bronchial asthma. Williams[375] has re-examined the figures contained in his previous articles, as outlined in the two previous reviews.[130,131] The *British Medical Journal*[6] commented editorially, "One of the perplexing facts about bronchial asthma is that some patients with severe asthma are like old soldiers and never die, whereas others succumb during comparatively trivial attacks." One must agree that it is important for the general practitioner to know how to detect the potentially dangerous case, even though he may search fruitlessly there and elsewhere for the methods of doing so.

Robertson and Sinclair[283] found the average annual death rate from asthma in England, Wales and Scotland to be 3,268 and another source[55] cited a similar figure, accounting for 0.6 per cent of all deaths. It is agreed that asthma starting in middle life more often becomes chronic and persistent with a poor response to therapy and a poor ultimate prognosis. Fatalities then are usually the culmination of a long series of severe bouts of status asthmaticus. That this is not always so was emphasized by Maxwell,[216] Earle,[78] Robertson and Sinclair,[283,284] and Houston et al.[161] The first-named observed nine asthmatic patients who died suddenly and unexpectedly in attacks not differing in any way from their customary paroxysms. The sudden deaths occurred without satisfactory explanation within a few minutes of the onset of what appeared to be an average attack. Medicolegal considerations were often troublesome subsequently. Each showed sudden failure of respiration. (The intravenous administration of nikethamide might be considered in such situations, according to Maxwell.[216]) Their ages ranged from thirty-seven to sixty-four years.

Asthma had been present for from six months to ten years, but six patients died within two years of the onset. There was little evidence of an allergic factor. Only one case had cardiac enlargement, but death was not attributed to heart disease.

Earle[78] contributed reports of fifteen fatalities, of which four were less than five years of age, and ten were between thirty-five and sixty years of age. Accordingly, death in the young adult asthmatic patient seems to be infrequent. Over half the patients had asthma less than ten years. Heart failure had little importance as an immediate cause of death in this series, and bronchospasm appeared to play a minor rôle. Death resulted from asphyxia produced by excessive mucous secretions blocking the air passages. Morphine played a part in two of the fifteen fatalities and aspirin may do so in the hypersensitive patient. Pulmonary infection was frequent but often difficult to diagnose. In a review of 160 fatal cases from the world literature, Earle found that 35 per cent died of uncomplicated asthma, 21 per cent with asthma as the chief cause, and 44 per cent, although asthmatic, died of other causes. More than one-half of the deaths compiled by Earle occurred between forty and sixty years of age. The chief complication was bronchopneumonia. Right ventricular hypertrophy was present in only fourteen of the cases.

In a series of eighteen fatal cases reported by Robertson and Sinclair,[283,284] the mode of death was sudden and unexpected in thirteen, but characterized by increasing exhaustion and terminal coma, with progressive anoxia and right heart failure in only five. Although some cases had contributory factors, asthma was the main immediate cause of death in all. The terminal attack lasted from a few minutes to twelve days, while the total duration of the asthmatic state varied from four days to thirty-five years. Nearly two-thirds of the deaths occurred in the months of September and October. The cause of the sudden fatalities in asthma, unlike those succumbing in prolonged terminal attacks, are not clear. Robertson and Sinclair speculate that a progressive rise in intra-alveolar pressure may quickly overcome the pulmonary capillary blood pressure of about 10 mm Hg, leading to a marked increase in the resistance of the pulmonary vascular bed which the right ventricle is unable to overcome, ending in rapid right ventricular failure, collapse and death. It is also possible that mucous plugging may occur fairly rapidly, the mucus being sucked deeper and deeper into the bronchial tree until impacted, with resultant suffocation. Houston et al[161] likewise found that death was sudden and without warning in all but two of their nine fatalities from uncomplicated status asthmaticus. The fatal attacks lasted from eighteen hours to several days. Only two patients received morphine during their final illness. While several had had paraldehyde, it is doubtful if it played much part. There was no clinical or pathologic evidence of respiratory infection or heart disease. Only four cases seemed extrinsic. Seven of the nine cases had been asthmatic for eight years or less, but all started in adult life. It appeared that death in status asthmaticus occurs especially in adult life and may occur with asthma of quite recent onset. Leu et al[200] described a patient who died suddenly (within a few minutes) of a not very severe attack, after a symptom-free period of two weeks' duration. The patient had had intermittent asthma for six months. The bronchial tree was completely obstructed with viscid mucus at necropsy.

The emphasis in several of these reports on the brevity and the unimpressive clinical features of the terminal episode, the relatively brief total

history of asthma in many instances, and the comparative youthfulness of some of the patients is in sharp contrast to generally accepted concepts. Further observations are in order, especially in this country. Equally warranted is a search for some common factor.

Three papers stress psychic factors as an important cause of death in asthma. In Maxwell's[216] series of unexpected asthmatic deaths, psychologic disturbances were present in all nine cases, and seven had expressed a conviction of impending demise. The author questions whether electro-convulsant therapy should be considered in the depressed asthmatic patient. Knick[185] found psychopathologic disturbances, principally neurotic and anxiety states, in all of seven fatalities in patients with asthma, and labels them as "psychogenic deaths." Four autopsies are reported in detail. In their eighteen fatal cases, Robertson and Sinclair[283] considered psychologic, allergic and infective etiologies, classifying them as primary or secondary. Psychologic factors were classed as solely present in five, as primary in five more (with allergic and infectious factors secondary in three and two cases, respectively) and as secondary (to infection) in two cases. Thus, two-thirds of their cases showed prominent psychic influences.

On the other hand, in thirty-one asthmatic deaths, Pearson[254] found infection to be the commonest factor for the whole group, but less so in the fourteen patients under the age of forty years, in whom allergic factors seemed more prominent. Aspirin played a contributory rôle in two instances and morphine in one. Autopsies in twelve cases revealed surprisingly little or no evidence of infection, even in those whose clinical findings during life suggested infection. Although infection seems important, especially in the older asthmatic patient, the manner in which it exerts its fatal effect is not clear. Like others, he found the duration of the asthmatic state was much greater in those dying before the age of forty years than in the older group.

Two deaths in a group of thirteen patients receiving cortisone for asthma were reported by Savidge and Brockbank.[302,303] Neither had responded fully to therapy. Reports of at least eight other asthmatic patients dying during either cortisone or corticotropin therapy were compiled from the literature. One other instance considered to represent corticotropin anaphylaxis was appended, the patient succumbing about eighteen minutes after a single dose of 25 units of hog corticotropin.

PATHOLOGY

Several of the reports mentioned in the previous section detailed the pathologic findings observed at autopsy. In the eighteen fatal cases studied by Robertson and Sinclair,[283] all showed mucous plugs in the bronchi and excessive activity of the mucous glands, and all but one, eosinophilic infiltrations in the bronchial walls; eight of them also had hyaline thickening of the basement membrane and hypertrophy of the muscle of the medium-sized bronchi. Nine of Earle's[78] fifteen cases revealed the usual findings and four had emphysema only. Of the complications, bronchitis occurred twice, enlargement of the right ventricle or both ventricles three times, and bronchopneumonia, pulmonary embolism, pneumothorax, and mediastinal emphysema once each.

Houston et al[161] were struck by the microscopic finding of extensive detachment of the ciliated bronchial epithelium in all cases examined. This partial or complete separation of the superficial epithelium left only a thin and generally single-celled layer of reserve or basal short non-ciliated cells

as a lining. It is assumed that in shorter attacks of asthma the detachment is not so complete, and after expulsion of the mucus, the bronchial epithelium regenerates. But in prolonged attacks an irreversible state may be reached, so that mucus can no longer be removed from the smaller bronchi because of loss of ciliary action and the attack will not respond to antispasmodics.

Halpern[145] discussed the physiopathologic mechanisms of the asthmatic paroxysms. He holds that asthma is a simple allergic disease, although granting that the allergic cause cannot always be demonstrated. The dyspnea and prolonged expiration, as well as the variability of other symptoms and of the response to therapy may be explained by the respective rôles of bronchospasm, bronchial edema and bronchial secretion. While the release of histamine accounts for many of the changes, antihistaminics are not effective; when bronchospasm is provoked by the presence of the bronchial secretions themselves, acting as a veritable foreign body in the bronchial lumens, the histamine liberation is of little moment in this phase.

CLINICAL PATHOLOGY

Modern therapy of asthma and the hypothesis of the general adaptation syndrome (Selye) have stimulated interest in the adrenal cortical function in asthmatics. Quarles van Ufford[261] studied adrenal function in 235 ambulatory and 100 hospitalized patients with asthma, and compared it with that in other allergic syndromes. Most asthmatic patients gave normal values, although 30 per cent had a negative Thorn test, compared to an incidence of 6 to 14 per cent in other allergic states. There was a slight correlation with the presence of an active infectious process, since more patients with an elevated erythrocyte sedimentation rate had negative Thorn tests. The urinary excretion of 17-ketosteroids was low or decreased in a large percentage of those suffering from asthma, more so in males than in females, but showed a similar trend in other allergic diseases. It was concluded that most asthmatic individuals have normal adrenal function and that steroid therapy cannot be considered as specific. Israëls et al[170] found the excretion of neutral 17-ketosteroids in bronchial asthma to vary with the age of the patient and with evidence of infection. Below the age of forty years, the excretion was significantly lower than in controls, while in females over fifty years of age, it was above normal. In asthmatic persons of both sexes, those with purulent bacterial bronchitis excreted more 17-ketosteroids than did non-infected cases; they also had lower levels of circulating eosinophils. Successful antibiotic therapy of the complicating purulent bronchitis almost always led to a considerable decrease in the urinary steroid excretion. These findings were attributed to the stress reaction produced by the infection.

Rose, Fyles and Venning[290] noted in a group of fifty-eight cases of obstinate asthma that the persistence of symptoms was not associated with a rise in the urinary excretion of glucocorticoids, as determined by biologic methods. With recovery, whether spontaneous (on bed rest and mild sedation) or on nonspecific therapy (intravenous typhoid therapy), the values rose, but much less than, for example, following severe trauma, surgery or burns. It seems that the asthmatic patient excretes less urinary corticoids than normal persons. The persistence of symptoms may be due in part to an inability of the pituitary or adrenal glands to augment the output of corticoids or to respond to the stimulus of the asthma. During attacks of asthma, the biologic urinary corticoids were on the average

below normal, but especially so in the intrinsic cases and those with the severer symptoms and more difficult to treat. This comparison was less striking in the extrinsic cases. The reason for the low values in many asthmatic patients is not apparent. Decreased adrenocortical activity is found in many chronic debilitating diseases. The degree of severity of asthma may be related in some way to adrenocortical activity and the ability of the adrenal to respond. It seems clear, however, that the tendency to become allergic is in no way related to adrenocortical function.

Gitelson[125] demonstrated in a case of asthma treated with small doses of corticotropin (10 units of the gel, intramuscularly, twice daily) that the blood pyruvic acid fluctuated inversely with the number of circulating eosinophils. Since hyperpyruvicemia occurs in many severe unrelated disorders and in states of emotional stress, it may be inferred that it is one of the nonspecific manifestations of the alarm reaction. Since epinephrine and the adrenal glucocorticoids enhance glycogenolysis and gluconeogenesis, respectively, there results an elevation of the concentration of the intermediary products in the blood, among them pyruvic acid. Gitelson is carrying out studies to determine if the blood pyruvic acid level and its response to corticotropin can be used to assess the function of the pituitary-adrenal system.

R. G. Mitchell and his co-workers[235] pointed out that histamine is excreted in the urine in two forms: (1) free, pharmacologically active histamine, and (2) conjugated, inactive histamine. The mean twenty-four-hour excretion of the free form was about normal in allergic children in a quiescent stage of the disease. During acute allergic episodes, the values were significantly lower. The administration of cortisone or hydrocortisone increased the urinary elimination of free histamine, but to abnormal levels in only two of five cases; the effect on the conjugated histamine was variable. These findings suggested that there is retention of free histamine during acute allergic episodes.

In response to a query[269] concerning a young child with infrequent attacks of asthma but a high and persistent eosinophilia, the possibilities of polyarteritis, parasitic infestations and hydatid disease, Hodgkin's disease, leukemia, tropical eosinophilia, and a persistent form of Löffler's syndrome were considered. It is thought highly probable that the function of the eosinophilic leukocyte is to carry histamine or a histamine-like toxic material from the bone marrow to the tissues for inactivation. Code et al[56] pointed out that basophils may also share the function of histamine carriage. Cortisone given to normal subjects caused a reduction in the number of basophils in a pattern very similar, although in a lesser degree, to the reduction in eosinophils. The parallelism is believed to indicate a relationship between the basophils and eosinophils, although whether this reflects a fundamental physiologic or functional association between the two types of cells is not established.

The constituents of pathologic bronchial secretions were studied by White et al[374] by means of direct phase-contrast and electron microscopy in conjunction with staining and chemical methods. The secretion of the ciliated mucous surface of the bronchial tree is considerably increased in asthma, chronic bronchitis and bronchiectasis. It was found that a proportion of hydrated fibrils of deoxyribonucleoprotein derived from the nuclei of degenerating inflammatory cells contributed to the structure of the viscid secretion during infective episodes.

The reliability of the results of sputum cultures may be questioned on

the basis of the studies of Bergman and Colldahl.[25] They compared the findings of cultures of the sputum and of secretions obtained by bronchoscopic aspiration in eighteen asthmatic subjects. In two-thirds of the cases, the bacterial flora recovered differed significantly in the two specimens. The findings of C. C. Brown et al[37] were roughly comparable. In twenty-one sputum specimens obtained from six cases of asthma, mostly of long standing and several complicated by acute bronchitis, pneumococci were present in one and *Hemophilus influenzae* in four, while the remainder contained no pathogenic flora. By contrast, the same bacteria were found in 73.5 and 50.6 per cent, respectively, of the sputum specimens from cases of bronchitis and emphysema. In half of these, pathogenic bacteria were present in both sputum and bronchial specimens, while in the other half they were recovered only from the sputum. Bronchoscopic aspirates in four of the asthmatic cases were free of pathogenic bacteria. Simultaneous nasopharyngeal cultures indicated that the organisms in the sputum are not derived from the nasopharynx during the process of expectoration. The authors feel that the low incidence of pathogenic organisms in asthmatic patients may be important if confirmed in a larger series. Of 400 sputum specimens from 300 unselected cases of asthma, Orie and Israëls[250] found ninety-nine to be purulent and bacteria-containing. *Hemophilus influenzae* occurred forty-three times, diplococci twenty-eight, *Neisseria* nine, and mixed flora eleven times. In the remaining cases, the sputum was mucoid and contained many eosinophils in 126 instances; mixed purulent containing mucus with many eosinophils and bacteria in thirteen; purulent but free of bacteria in fifty-two; mucoid without bacteria or eosinophils in eighty-nine instances; and no sputum available in twenty-one cases. However, the quality of the sputum was often variable in the same patient, ranging from purulent to mucoid eosinophilic at different times. The interpretation of these findings will be considered in a subsequent section.

Livieratos, Danopoulos and Maratos[202] presented evidence indicative of functional impairment of the reticulo-endothelial system in patients with bronchial asthma. Assuming that the reticulo-endothelial system is the main tissue burning alcohol, the alcoholemic curve after the ingestion of a measured amount of alcohol will reflect its function, and will be higher than normal when reticulo-endothelial function is impaired. Such curves were found in eight cases of asthma. Its height did not correlate with the intensity of the dyspnea. By contrast, the alcoholemic curve in emphysema with marked dyspnea was normal.

CLASSIFICATION

Several attempts at orderly classifications of asthma have recently appeared. Although they agree on some points, the considerable differences of attitudes and opinions expressed serve to point up the extensive areas of inadequate knowledge of the disease and the need for objective criteria in evaluating the varying findings presented by different patients. Swineford[335] takes the stand that since asthma is a syndrome characterized by wheezing, any narrowing of the airways causing wheezing should be called asthma, particularly if it is accompanied by wheezing. The causes of wheezing are numerous, but they may be classified with reasonable accuracy by means of the patient's history and physical examination. Most asthma sufferers owe their disease to multiple causes. Skin testing is helpful only in the detection of atopic (allergic) causes of wheezing. A

review of previous classifications leads to confusion. Salter's classification of 1860 had much to recommend it. The "intrinsic" classification (Rackemann) may be objected to for a number of reasons. The term "bronchial asthma" is itself redundant, since no other structure wheezes.

Swineford groups the causes of asthma as follows:

Group I: atopic (allergic) and infectious.
Group II: reflex, psychogenic, physical, and chronic lung disease.
Group III: cardiac, bronchial obstruction, and idiopathic.

He suggests that perhaps the idiopathic type should be placed in a separate fourth group and in a more recent study,[338] has done so. Most asthma is due to atopy or infection, or a mixture of the two. Numerous differences between the two are presented. Infectious asthma in pure form is less common than the atopic form. The patient with atopic asthma coughs himself out of an attack, while one with infectious asthma coughs himself into an attack. Differences in the sputum, sinuses, appearance of the uvula, and response to treatment are emphasized. When atopy and infection are controlled, the Group II causes, which are usually present in chronic asthma and which are more likely to aggravate asthma from atopy and/or infection than to be primary causes, usually become unimportant.

Comments on the other types must, of necessity, be brief. Reflex asthma usually relates to nasal polyps, less often to thyroid nodules, carcinoma of the lung, and aspiration of foreign bodies. Physical allergy may be diagnosed when attacks are attributable to exposures to heat or cold, temperature changes, drafts, wet feet, hot or cold baths, or abnormal humidity. Confirmation is achieved by physical tests, although physical allergy is rarely the chief cause of asthma. Chronic lung diseases causing asthma include emphysema, fibrosis and lung cysts. Psychogenic influences vary from time to time even in the same patient. They may be difficult to detect. Several points in the patient's history, life situation, behavior, appearance, and response to therapy may clarify the relationship. The only convincing proof of cardiac asthma is relief from the treatment of heart failure. The response to morphine or epinephrine does not serve to differentiate. Paroxysmal nocturnal orthopnea should not be called cardiac asthma unless there is wheezing. Bronchial obstruction with wheezing may result from foreign bodies, polyps, adenomata, cancer, kinks from contracting scars or expanding cysts, and external pressure from mediastinal or peribronchial masses.

Brown and Halpin[42] present a plea for a classification analogous to that used by the cardiologists for heart disease. Taking wheezing as the predominant sign and symptom, one should consider the etiology, anatomy, and physiologic and functional derangements. At least eight clearly defined syndromes are denoted:

1. Atopic
2. Infectious: (a) acute, (b) chronic
3. Psychogenic
4. Physical
5. Nasogenic (or reflex)
6. Cardiac
7. Locally obstructive
8. Asthma due to drug and chemical reactions, noxious vapors and fumes.

Each type has its own characteristics with regard to the personal and family history of atopy, type of onset of wheezing, clinical course, physical examination, pathologic findings, laboratory data, skin tests, and response to treatment. It is granted that the categories can and do, overlap. Allowance is made for adding specific terms concerned with anatomic and physiologic changes. Degenerative, fibroblastic and obliterative changes may be superimposed. Status asthmaticus is best regarded as separate from the others, not only in degree, but in type. The severity of asthma is classified as grades 1 to 3, depending on the symptomatic response, the degree of exposure, the speed of recovery, the type of remedial agents required, the interval findings, and the pulmonary function studies. Typical descriptive diagnoses using this code might be "asthma, ragweed, with acute infection, class 2" or "asthma, infectious, chronic, with emphysema, class 3." No finality is claimed for this classification scheme, but the advantages of clear terminology are emphasized.

At a two-day meeting[100] in Italy, Lusena re-affirmed the allergic origin of true bronchial asthma in most, if not all, cases, as distinguished from dyspneas of various origins. Most cases of bronchial asthma are due to an inhaled allergen, some are caused by foods, and a few by drugs. Some foci of infection, usually located in the teeth or tonsils, may condition an allergic mechanism. Duchaine of Brussels at the same meeting[100] and in a subsequent article[74] emphasized that since there are a multiplicity and diversity of causes responsible for asthma, therapy should be guided by a direct appreciation of the varying degree of each. Asthma may be classified as nervous, endocrine, allergic, tuberculous, and infectious. It should be distinguished from the "autonomous" form of a respiratory syndrome characterized by paroxysmal dyspnea but caused by chronic bronchitis or essential emphysema. Rather than subdivide asthma into purely allergic asthma, secondarily infected allergic asthma, bacterial asthma, and asthma of unknown cause, it would be more profitable to substitute the concept of "allergic charge" or "allergic load" to encompass all the various asthmogenic stresses. Rapaport[272] likewise recommends an awareness of the multiplicity of possible causes of asthma and attempts to evaluate them, even when the patient is under treatment. Several or many of the immunologic and nonimmunologic factors may coexist and interact in the same patient. Statistics are presently unavailable on the relative incidence of the various causes of asthma. However, atopy and infection are usually the most significant primary factors.

Williams[375] recognizes an essential interdependence of the allergic, psychologic, and infective factors, but suggests an assessment of their relative importance at different age levels. In infants and children to the age of approximately four years, the infective factor is usually dominant, since bronchitis is so common; the allergic factor, especially with regard to foods, is often important; and a "nervous" mother affects the child. From the ages of five to fourteen years (approximately), the infective factor is of decreasing importance; the allergic and psychologic factors are important, the latter often demonstrated after excitement, such as parties or when the patient is overtired; the child is often insecure. In young adults, between fifteen and twenty-five years of age, the allergic factor is dominant, the psychologic factor insignificant, especially in males, and the infective factor absent, except in some chronic cases. In all these age groups, a positive family history of allergy tends to be prominent, whereas in older persons it is not so common. In middle-aged and elderly patients,

the allergic factor becomes less important with advancing age, except for those whose condition is worse in the summer and better in the winter. In females in this age group, the psychologic factor is often very important, and frequently dominant, including overwork, overworry, often obesity, and loss of morale. In males, it is also often quite important, but not so dominant as in females. In both, the infective factor is common and increasingly important with age (often with increasing eosinophilia), but usually more dominant in males.

Hunt[165] classifies chronic asthma as involving, in addition to a suitably susceptible "soil," five exciting factors: (1) infective: usually respiratory; (2) allergic: of little import, since it is doubtful whether foreign proteins alone play a great part unless the mucosa has already been affected by acute or chronic infection; (3) gastrointestinal: as by overeating; (4) reflex: mediated by the vagus and exemplified by an attack on seeing a motion picture of horses; and (5) neurogenic: produced by "discharges" from nerve cells in the cerebrum or brain stem, comparable to epilepsy. The last type may be helped by barbiturates.

Turiaf[351] introduced a category of "asthma with continuous dyspnea" which he terms "pernicious asthma" since it remains inaccessible to all therapies except corticotropin and cortisone. It is commoner than usually thought, is often misdiagnosed, and produces pulmonary cripples. It affects all age groups, but is unusual early in life and commoner after fifty years of age, and somewhat more frequent in males. Multiple bronchial stenoses and dilations are frequently present—often in a single case. Although it is never a purely allergic asthma, house dust, molds and pollens may aggravate it. Occasionally, there is a tuberculous element. It is often unfavorably influenced by the immoderate usage of sympathomimetic drugs. It must be differentiated from bronchial malignancy, cardiac decompensation, bronchiectasis, and idiopathic pulmonary emphysema.

ETIOLOGY

It is apparent from the material just reviewed that the etiology of asthma is multiple, and often so even in a single patient. Accordingly, any subdivision of etiologic factors is arbitrary. Nevertheless, it is deemed more feasible to follow the customary categories.

The problem of nonallergic asthma has been considered by Stuppy.[331] Of unknown etiology, it shows relationships to the release of H-substance, emotions, respiratory infection, and intrinsic mechanisms. It occurs mostly past forty years of age, and without specific allergens. It leads more frequently to intractable asthma or status asthmaticus than does the allergic form. Allergic asthma may, after a long symptom-free period, be followed by nonallergic asthma. The sputum is usually purulent, yellowish, viscid and gelatinous, containing many leukocytes, bacteria and a smaller number of eosinophils. The pathology and the results of pulmonary function studies differ from those of the allergic type.

Waldbott[369] has again directed attention to anaphylactic pneumonia, a serious and often misdiagnosed condition, which occurs in patients who have not had asthma before and which is not infrequently followed by the development of subsequent asthma. Of 100 consecutive cases of asthma starting before the age of six years, fifty-two had a pneumonic process preceding the onset of asthma. While some of these were really infectious pneumonia, a good proportion seemed to have a prodromal period of shock. This syndrome differs markedly from the types of pneumonia complicating

asthma. It occurs chiefly in children. Death is not infrequent. Causes include inhalants, ingestants and thermal changes, as well as injectants. One three-year-old child had sixteen episodes of anaphylactic pneumonia in a period of two years before true asthma developed.

An Army group headed by Huber[162] has made available further information concerning "Yokohama asthma" (or as they prefer to call it, a new environmental respiratory disease), which they consider a "peculiar" type and which was mentioned in a previous review.[131] It has been observed only in the winter months in military personnel in Yokohama and Tokyo, but occurs elsewhere in Japan. It has been known to affect indigenous Japanese and Europeans in the same areas, as well as children. It appears to consist essentially of recurring nocturnal asthmatic paroxysms, and half of the 200 cases studied eventually developed status asthmaticus. It is often resistant to therapy, and fastness to epinephrine or aminophylline developed rapidly. Removal from Yokohama always gave relief. The condition is apparently not due to pollens or molds. It occurs in highest incidence in proximity to a harbor, usually surrounded by low hills, sundry manufacturing facilities, and occurrence of "heavy smog" during the winter months. Preliminary atmospheric data indicate a correlation of the incidence of the disease with the concentration of air contaminants (particularly ether-soluble aerosols and dust) and with smog.

Markow and Reicher[210] studied the effect of meteorologic factors on the symptoms of ninety perennial asthmatic patients for a period of two years. Since daily observations were too confusing, monthly averages were followed. About half the cases had seasonal hay fever, and most of the remainder had aggravation of the asthma during the pollen season. Hyposensitization with pollens, house dust, stock vaccine and *Alternaria* was given when indicated. The daily incidence of asthma ranged from 4 to 17 per cent. The monthly variations showed peaks in January and May, and fewest attacks in July, with a low rate between June and September. The curves for the two years were closely parallel. The attack rate was compared with monthly averages of outdoor temperature, relative humidity, barometric pressure, and total rainfall; also with the incidence of upper respiratory infections and the ragweed and *Alternaria* counts. There was no definite correlation with weather conditions, but a trend was observed regarding temperature, humidity and rainfall. Less asthma occurred when the monthly average temperature exceeded 60° F. There was a rough relation between temperature, respiratory infection and asthma, but no clear-cut cause and effect. Unexpectedly, the period of highest average relative humidity, from May to October, corresponded with the lowest incidence of asthma. No definite trends were noted with regard to barometric pressure, but there was often a decrease in asthmatic symptoms in the group when the average barometer reading fell below and remained below 30.00 inches. Symptoms increased with rising *Alternaria* spore counts but not with ragweed pollen counts, perhaps because of specific therapy. It is concluded that, despite previous ideas, seasons of high humidity and increased precipitation are not incompatible with the well-being of perennial asthmatic patients under therapy.

In the Hawaiian Islands, "Kona weather" is accepted by many physicians and patients as a cause of asthmatic attacks. Cyclonic storms, called "Kona storms" locally, bring southerly streams of warm, moist tropical air, often accompanied by a steady rain. During this time there is little diurnal variation in temperature, relative humidity or winds. Such storms

rarely last more than three or four days, but are often preceded and followed by an oppressive stagnancy. According to Myers and Price,[244] the onset incidence of 1,259 paroxysms in children was a little greater during Kona weather than at other times. The difference, while statistically significant, was small. Sharp peaks in incidence and asymptomatic days were no more nor less frequent than at other times. In twenty-six asthmatic children studied in detail, no particular weather type invariably preceded the attacks. In most instances, only a chance relationship appeared to exist between an attack and the concurrent or preceding weather conditions. The problem of weather analysis is a difficult one, with many limitations in the present state of knowledge, and attempted correlation with asthmatic attacks interposes further obstacles. It may be noted in passing that the maximum incidence of attacks in asthmatic children in Hawaii occurs between October and May, with a yearly peak in January, February and March. There is some suggestion that respiratory infection is the predisposing factor in this.

These last two reports point up the need for intensive and carefully controlled studies on possible meteorologic influences on asthma, and the abandonment of preconceived and hasty opinions on the part of both physicians and patients in this connection. The latter have a stultifying effect on a more detailed search for other causative and precipitating conditions for the paroxysms. Climatotherapy will be considered in the section on Treatment.

Inhalant and Occupational Asthma.—Lest, in our search for new and unique allergens, we forget the customary, Vallery-Radot and others[366] remind us that ordinary house dust is the most frequent cause of asthma. It is followed, among the inhalants, by feathers, danders, pollens, wool, molds, flour, cotton, kapok, silk, and wood dust, in approximate order of frequency. Dust asthma is often associated with allergy to bedding and infections of the upper respiratory tract or bronchi. It is characterized by increased frequency of attacks at the start of cold weather when the heat is first turned on, and by improvement at the seashore or high altitudes. Definitive treatment involves desensitization, and good results may be expected. Fewer therapeutic failures occurred when an extract prepared by the dioxane method (Endo) was employed than when a Dutch preparation was used. Avoidance of environmental allergens, the use of hypoallergenic bedding, and the treatment of associated infections are also helpful. Engelsher[88] recalls that he has seen a few asthmatic patients, including a case of feather asthma, institutionalized under a mistaken diagnosis of active pulmonary tuberculosis.

Evaluation of the methods of removing dust and other particulate allergens from the air has quite properly been accorded attention. Harsh[151] studied the efficacy of thirteen different commercial vacuum cleaners falling into five general types. The amount of dust, mold and bacteria which escaped from the exhausts varied markedly but still was very small, even at worst, compared to the total amount of dust removed. No significant differences occurred among any of the models in the amount of dust which settled out from the air in the room during and after the tests. It would seem advisable for the house dust-sensitive housewife to wear an efficient filter mask when using any type of cleaner herself. For those patients who can be absent during and for a short while after the cleaning, the only important factor is the thoroughness of the dust removal.

Friedlaender and Friedlaender[106] demonstrated the effectiveness of a new portable and relatively inexpensive room-sized electrostatic precipitator unit (the Raytheon Micronaire) which requires no special installation. Electrostatic air cleansing of airborne allergens, dusts, smokes and irritants is superior to mechanical filtration, but the large size, expense and elaborate installation of previous electrostatic equipment have limited its usefulness. While the new apparatus failed to yield as good therapeutic results in a series of nonseasonal asthma cases as in pollen asthma, the effect was still beneficial. Air-cooling and air-conditioning *per se* apparently do not add to the effectiveness of efficient air-cleansing. Wider application of electrostatic precipitators in the management of environmental inhalant allergy is envisaged.

It was recently pointed out[262] that air cleansing devices can be considered only as adjuncts to the total care of the allergic patient. Removal of drapes, curtains and rugs, damp wiping of walls, ceilings and floors, and hypoallergenic bedding are often necessary. With regard to dust- and pollen-sensitive cases, it is impossible to predict in an individual case how much relief will be afforded by either the simpler fan driven air-filtering devices or the more complete air-conditioning units. The necessity for leaving the room in the course of daily activities may be a determinant factor. Kinkade[183] has evaluated the influence of air-conditioning in respiratory allergies and in otorhinolaryngologic conditions.

An "epidemic" of bronchial asthma in Baurú, Brazil, was reported by Mendes and Ulhôa Cintra.[223-225] In a few days, 150 cases and nine deaths occurred in a town of 60,000 population. The symptoms were violent and of sudden onset, and were decreased or controlled by rain. Removal of the patients to a town nine miles away always relieved. A number of patients had asthma for the first time during the "epidemic." The cause proved to be allergy to castor bean *(Ricinus communis)*. A castor bean crushing mill, in changing its methods, discharged from its ventilators to the outside air a large part of the castor-bean residues. The cases were confirmed by skin testing with castor-bean pomace, passive transfer, and the inhalation of an aerosol of the extract. When the mill ceased operations, the symptoms disappeared, but recurred when the mill resumed later. A change in the method of extraction, with the dusts caught in a water reservoir, solved the problem.

Ratner and his co-workers[275] mentioned the case of a woman who became sensitized to soybean dust emanating from a soybean processing plant opposite her home. She was forced to move in order to avoid the asthma and abdominal distress caused by the soybean dust in the air, but remained sensitive to the ingestion of soybean as contained as a filler in bologna. Among 1500 employes in a plant devoted to processing soybean products, only two cases of asthma due to the inhalation of soybean dust and fumes in the air were discovered in a period of seven years.

Weaver[372] discussed the problem of asthma in industry. The attitudes of the industrial allergist differ somewhat from those of his colleagues in private practice. The job environment and specific sensitization to dusts, fumes, and gases are of crucial import, as exemplified by "baker's asthma" and "miller's asthma." Such cases are uncommon, and barring effective desensitization, the employe must be removed from his peculiarly noxious environment. However, in a refinery and petrochemical plant with 7,500 employes, Weaver, by means of direct skin testing, controlled exposures to suspected dusts and fumes, and sometimes pulmonary function deter-

minations before and after exposure, failed to discover even one example of true occupational asthma. While industrial dusts and fumes (especially acid fumes) acting as primary irritants may be well tolerated by normal individuals, they may have devastating effects on the asthmatic patient, dramatically precipitating attacks. An effort should be made to identify all significant industrial irritants and to define their areas of exposure. This will allow appropriate job placement, taking into account the worker's special skills and his psychologic responses. Absenteeism of asthma sufferers can be greatly reduced by proper allergic therapy. Disability retirement is never indicated for uncomplicated paroxysmal asthma, but is necessary for a relatively few industrial respiratory cripples, because of emphysema and chronic pulmonary disease associated with bronchial asthma.

Brown and Colombo[41] also reported on asthma in industry. Of the estimated eight million asthmatic patients in the country, approximately three million work. The job environment, the home environment, and exposures in transit must all receive consideration. There may be a cumulative effect due to overlapping exposures, with a pattern of wheezing for the first hour or two at work, and again for the first hour or two after returning home. Numerous allergens, of course, are contacted in industry, and are usually well known: wool, cotton, kapok, furs, castor bean, gum acacia, raw coffee, hemp, jute, molds, smuts and rusts may be mentioned, as well as the nonspecific aggravation from nonallergenic gases, odors or fumes. Longshoremen, truck drivers, and workers in mattress and furniture factories, woolen mills, and pharmaceutical plants have been seen with asthma. Air conditioning or air purification may, to a certain degree, solve the problem of inhalant allergens. Industrial conditions are often unjustifiably blamed by the worker, sometimes for reasons of compensation, until it can be shown that they play little or no part in the condition. Psychogenic factors at the job may be of great significance. The industrial physician is in a favorable position to study these problems, to evaluate the effects of the work environment, and to arrange for the removal of industrial causes of asthma.

Mechaneck[220] reported the first case of asthma and allergic rhinitis caused by sensitivity to locust bean gum dust. The exposure was occupational and symptoms occurred only in the plant. Attempts at hyposensitization by both subcutaneous and nebulization routes failed, reactions occurring with the greater concentrations by both methods. Air-conditioning of the laboratory where the patient worked controlled the symptoms. Locust bean gum, derived from the carob or locust bean tree (*Ceratonea saligna* L.), is a hemicellulose known by many names, including crab gum, carob seed gum, swine's bread, gum hero, lakoe gum, rubigum and tragasol. Previous reports of hemicellulose sensitivity have implicated gum acacia (gum arabic), karaya, and tragacanth. Other hemicelluloses in commercial use include kernal gum, guar, lichens such as Irish moss, and extracts of the seeds of quince, psyllium, and flax.

Fuchs[112] reported eight cases of spastic bronchitis and asthma among weavers in a silk plant. Six of them reacted to sericin, the ground substance in raw silk, rather than to the silk fiber itself, and passive transfer was positive. One asymptomatic weaver also gave a positive intracutaneous reaction. Dyers and other workers in the same plant apparently were not exposed in the same manner.

According to Turiaf and Cabail[354] only two reports of bronchial sensi-

tization to formol have appeared. They added a case in which exposure took place in a match factory where formol was used to harden the tips of the matches. Provocative inhalation of the vapors of a formaldehyde solution, however dilute, caused severe asthma. Charpin[52] attributed the asthma of a worker in a physiology laboratory to the skin emanations of the frogs used in the experiments. Attacks were always nocturnal, but did not occur on week ends and vacations. While skin tests with dust and molds from the laboratory were negative, both direct skin testing and passive transfer tests with an extract of frog skin were strongly positive—but only with the species of gray frog involved and not with the common garden frog. If the laboratory will not change the type of frog used, Charpin intends to desensitize the patient.

Prickman and Peters[259] described the case of a housewife convinced that she was allergic to her husband. Asthmatic attacks occurred when he came home in the evening or even when he visited her at her parents' home. He worked in a grain elevator and skin testing showed that the patient was allergic to rye. Having the husband shower and change clothing before coming home solved the problem.

A farmer observed by Colldahl[58] had seasonal asthma, conjunctivitis and rhinitis in May for about one month. This is thought to be the first case due to rape *(Brassica napus)* pollen or to any species of the *Cruciferae* family.

Tobacco smoking, so much in the medical news in other respects, has received attention in relation to bronchospasm, bronchitis, emphysema, and its influence on ventilatory function. Greene and Berkowitz[134] studied tobacco bronchitis from the anesthesiologist's point of view. Smoking leads to cough and tracheobronchial hyperirritability and hypersecretion, predisposing the surgical patient to spasm of the bronchi, larynx and respiratory muscles, bronchorrhea, atelectasis, pneumonia and such complications as wound dehiscence and incisional hernia. It is a most important cause of bronchospasm and bronchorrhea during and after anesthesia, regardless of the type of anesthesia. Other causes of bronchitis in their experience were acute upper respiratory infections, occupational exposure to inclement weather or dust, emphysema, asthma, obesity, bronchiectasis and silicosis, but smoking was several fold more common than all other causes combined. Tobacco bronchitis was rare in cigar and pipe smokers. It was the most frequent factor in the etiology and pathogenesis of the complications that follow bronchitis of any origin: laryngospasm, bronchospasm, and bronchorrhea during anesthesia, bronchitis, atelectasis and pneumonia after operation. Greene and Berkowitz agree with previous reports that pulmonary emphysema is unusually frequent in inveterate smokers with marked bronchitis.

Maurer and Spain[215] discussed the evidence for tobacco smoke as both a secondary irritant and as a primary sensitizer in patients with asthma and allergic rhinitis. Whether or not one accepts the concept of an allergy to tobacco, it is important as a toxic agent or as a primary or secondary irritant. In asthma, avoidance of smoking cannot be stressed strongly enough. The bronchial membranes are extremely sensitive to such irritants as smoke, dust, fumes, cold air and pungent odors, so that smoking must increase the cough and asthma if continued for any length of time. No patient with asthma should further irritate his inflamed membranes with smoke just because tests for allergy to tobacco have given negative results.

Hansel[147] and Carryer et al[49] are in general agreement with this point of view.

Micheli[226] found smoking to cause a marked constriction of the bronchioles, sometimes of sufficient degree to produce a functional atelectasis of some parts of the lung. Later, emphysema may develop with or without bronchitis. The local irritation of the bronchi caused by the tobacco smoke is non-specific, resembling that from any other dust or smoke; however, the quantity and duration of exposure differ. Of 1,522 smoking physicians in New Jersey questioned, more than one-fourth reported cough resulting from smoking and nearly one-tenth had wheezing, according to Rosen et al.[291] Numerous other complaints occurred with varying frequency, including nasal symptoms in 19 per cent.

In an acute experiment, Bickerman and Barach[27] determined the effect of the leisurely smoking of three cigarettes in ninety-one cases of intractable asthma and hypertrophic pulmonary emphysema of the bronchospastic type. All were mild to moderate smokers. There were, on the average, no noteworthy changes in ventilatory function as determined by a battery of pulmonary function tests. Smoking may have increased the bronchospasm in ten cases showing a reduction of vital capacity and maximum breathing capacity. In no case, however, was a clinically perceptible paroxysm of asthma produced nor did the subjects complain of subjective symptoms. In nine of the patients showing an increased vital capacity and maximum breathing capacity, the smoking had caused a cough productive of mucoid or mucopurulent sputum, with presumably more efficient alveolar ventilation due to the elimination of the mucous plugs. However, most of the thirty-eight cases who had increased cough as a result of the smoking showed no significant change in the functional tests. It must be noted that these acute observations have no bearing on the question of the effects of habitual smoking on respiratory function.

The significance of fog and smog in increasing the morbidity and mortality of chronic respiratory diseases has been of great moment to the British.[99,175] While no one constituent of the fog can be incriminated, the products of the combustion of coal and especially sulfur dioxide and trioxide seem to be of prime importance.

Molds and Fungi.—Richards[280] pointed out that in houses which are visibly moldy, as on walls, books, leather articles or textiles, the mold spore content of the air differs in type and in numbers from that of the outside air. Most commonly found in such situations in Wales (not in order of frequency) were *Alternaria tenuis*, three species of *Aspergillus*, *Cephalosporium acremonium*, *Cladosporium herbarium*, several species of *Penicillium*, and *Pullularia pullulans*. The predominant species varied from one house to another and even from room to room. Spore cultures in and adjacent to a dry, clean dwelling yielded an outdoor catch more than five times as large as that indoors, and uniformly larger for each genus, with the same molds in approximately similar proportions at both sites. Most common were *Cladosporium*, sterile mycelia of white-forming type (probably *Oospora*- and *Basidomycetes*-like), and *Penicillium*. These along with *Pullularia*, *Aspergillus*, *Phoma*, *Botrytis*, *Epicoccum*, and *Oospora* accounted for 90 per cent of the total catch. While *Cladosporium* predominated from June to October, *Penicillium* was dominant the remainder of the year and showed little perennial fluctuation. A partial explanation of the varying ratios of the catch of individual species indoors

and outdoors may rest in differences in spore size and in their relative need for moisture.

Williams[375] stated that the dominant mold spore in Britain between June and September is *Cladosporium,* accounting for 50 per cent of the total spore catch, but of lesser importance in large towns. Of 500 asthmatic patients tested with *Cladosporium,* 10 per cent gave positive reactions, and it was the principal cause of the disease in about 2 per cent of unselected cases.

Maunsell[214] noted that mold-sensitive patients have exacerbations on spring-cleaning or moving, or during redecoration or structural repairs. Some cases of allergic rhinitis have their first paroxysm of asthma at such times. Maunsell found that fungus spore cultures were ten to twenty times greater in rooms in houses where structural repairs or rebuilding were in progress, as compared to "undisturbed" rooms. The rise was due chiefly to *Penicillium,* followed by yeasts and *Cladosporium.* It is reasonable to recommend that mold-sensitive patients stay away from home during periods of redecoration or structural repair, whether or not the patient's own room is involved.

Studies on dry rot *(Merulius lacrymans)* as previously reviewed[130,131] have been extended by Richards.[279] Dry rot can sporulate at any time of the year, but asthma due to the inhalation of the spores is more likely in the latter part of the year. Slide methods showed that large numbers of spores are readily carried through the house by air currents. Dry rot, under certain conditions, may be present for several years without producing fruiting bodies, so that spores are not always found in the presence of rotting wood.

Credille[62] reached the conclusion that the generally unsatisfactory results of hyposensitization therapy with molds is explained by the more rapid elimination of molds from the body as compared with pollen. In animal experiments, in reverse passive transfer studies, and in subcutaneous injections in control subjects challenged with specific reagin-containing serum, it was found that *Alternaria* extract was eliminated 2.5 to 6 times as rapidly as ragweed extract. Accordingly, a more intensive mold therapy was employed, and yielded better results than in previous seasons.

A case of asthma apparently due to *Candida (Monilia)* was reported by Sclafer.[308] The asthma started after hospitalization for a tuberculous serofibrinous pleurisy for which antibiotic therapy was employed, and was characterized by daily attacks and premenstrual exacerbations. Since *Monilia* was not recovered from the sputum, Sclafer assumed that the allergen was absorbed from the intestines. The evidence for the diagnosis lay in the intense skin reactions to high dilutions of monilial extract (even a 1:3,000 dilution), the aggravation of the condition after injections of the extract, and the control of asthma by desensitization with small dosage. Malamud et al[208] saw seven cases of status asthmaticus in whom cultures of sputum yielded *Monilia.* Iodide therapy was usually effective.

Food.—Clein[53] reviewed the question of cow's milk allergy in infants. Milk allergy is a common cause of multiple allergic symptoms in about 6 to 8 per cent of infants fed artificially. While asthma is not usually the first sign of allergy in an infant, it occurred in fifteen cases out of a series of 206 infants sensitive to cow's milk. A one- or two-day trial period of complete elimination of cow's milk and the substitution of a soybean preparation will quickly determine whether or not milk is the guilty factor. It

may be noted that many would prefer a longer trial period. If the symptoms are completely relieved, the infant should be continued on soybean milk for at least four months.

In the interests of impartiality, attention should be called to Glaser and Johnstone's reply[126] to the critics of their recommendation that soybean feeding be employed from birth in potentially allergic infants, since the criticisms were previously reviewed.[131] It is claimed that the procedure reduced the incidence of the subsequent development of major allergies from 60 per cent in the control groups to 15 per cent in the experimental group. Further study is certainly in order. Ratner et al[275] confirmed the weak allergenicity of soybean protein. Soybean oil and soybean sauce proved to be nonallergenic. While untreated native soybean protein was shown to pass readily through the intestinal wall in an unchanged state, it rarely produces allergic manifestations. Even this low degree of antigenicity could be further reduced by processing the soybean protein by adequate heat in the presence of moisture. This may be attributed either to a change in the protein molecule or to a reduction in the solubility of the protein in the intestinal tract. An asthmatic infant, exquisitely sensitive to milk proteins, was found to thrive on a soybean substitute. The few cases of soybean allergy in the literature apparently acquired their sensitivity through prolonged inhalation of soybean dust rather than through ingestion.

A recent Query[267] concerned a five-year-old child so allergic to fish that hives and asthma develop when she smells fish or enters a room in which fish has been fried. One must agree with the answer that desensitization is not indicated.

Infections.—All shades of opinion regarding the significance of bronchial infection in asthma have been recorded in the past year and it is impossible to reconcile them. Jiminez Diaz and Arjona[172] hold that 80 per cent of asthma is nonallergic in the sense that exogenous causes cannot be demonstrated, and most of these seem to be infectious or bacterial. The development of infectious asthma can be divided into three periods: (1) paroxysmal, (2) persistent, and (3) angiovisceral. The first stage resembles allergenic asthma in many respects. The second stage is characterized by continuous symptoms, with exacerbations resulting from atmospheric or climatic changes, the inhalation of fumes or dust, psychic influences, and further infection. Not all patients reach the third stage since death may supervene from infectious complications or circulatory disease, but it includes collagen (fibrinoid) degeneration, nephritis, hypertension and vascular allergy. The therapeutic connotations justify antibiotic therapy, either prophylactically or phylactically, vaccine filtrates, and purified bacterial proteins.

From the standpoint of a bronchologist, Davison[66,67] feels that the infectious factor is the most frequently overlooked and undertreated factor in chronic asthma. Asthma beginning after forty years of age is usually due to infectious bronchitis. High eosinophil counts occur in the blood and bronchial exudates of patients with infectious asthma. Adequate management requires the elimination of all foci of infection. In a series of fifty cases, thirty-three had chronic suppurative and hyperplastic sinusitis, and this usually requires surgical attention. Löffler's syndrome occurred four times, pulmonary fibrosis five, and bronchiectasis three times. Bronchoscopic aspiration is often helpful. Autogenous vaccine therapy is frequently effective.

Frouchtman[110] found no specific differences in the bronchoscopic examination of twenty-eight cases of bacterial asthma, of six cases of asthma secondary to bronchial suppuration, and of eight mixed cases. In most instances, the inflammation was localized and was considered to constitute an irritative focus maintaining a state of endobronchial irritability. The symptomatic response to the bronchoscopic aspiration of the secretions and the instillation of epinephrine was said to confirm this view, as did the histopathology in ten biopsied cases. It is conceived that the bronchial infection, rather than actually giving rise to bacterial allergy may, by reflex effect, cause bronchial spasm both locally and at a distance.

Spoujitch and Danilovitch[325] express the view that infection plays an important part in the pathogenesis of asthma, but that the relationship is complex. Bacteria sometimes (though rarely) act as allergens, while in other cases their presence favors the absorption of other allergens, or constitutes a factor determining the localization of the shock tissue. (These views may be compared with those of Frouchtman given above and with the experiments of Gross[139] described in the section on Experimental Asthma). Sometimes all these actions take place simultaneously. In any event, the early treatment of bronchitis in each case of asthma, before the appearance of chronic irreversible bronchitis, is paramount.

Hosen and Carabelle[160] state that infection is more frequent in allergic respiratory disease in patients less than two years old than it is in older children and adults. In general, favorable results were obtained with specific antibiotics, selected according to the results of bacterial sensitivity testing. But asthma with infection was less favorably influenced than, for example, allergic sinusitis or asthmatic bronchitis in which good results were about three times more frequent.

The investigations of Prigal[260] revealed that chronic sino-respiratory infections are contagious within the family group. The hemolytic streptococcus was the most frequent offender. Infections of the skin and eye of the patient and/or relatives may act as a focus for infection and reinfection of the respiratory tract. Appropriate antibiotic therapy and hygienic measures will do much to prevent dissemination of such bacteria within the family group.

So-called intrinsic asthma in the elderly patient is frequently infectious. While Forman and Blatt[103] feel that positive tuberculin-like reactions to bacterial vaccines are often significant, they may not reflect the present status of the patient. They therefore employed the Blatt-Nantz test to detect bacterial allergy. The test consists of suspending the leukocytes of the patient in filtrates of various strains of bacteria and determining the number of white blood cells damaged or killed after seventeen hours' incubation. If a considerable number are affected, it is taken to indicate an allergy to the particular strain of bacteria from which the filtrate is derived. The method was found of value in intrinsic asthma and in the elderly atopic patient whose asthma, over the years, became complicated by bacterial allergy. A number of patients were improved or rendered asymptomatic by therapy with carefully graduated dilutions of the filtrates from offending organisms selected on the basis of the test. It is claimed that in this way a specific desensitizing agent is available in intrinsic asthma.

On the other hand, the study of 400 sputum specimens from 300 unselected cases of asthma, as previously outlined, convinced Orie and Israëls[250] that there is no justification for subdividing asthma into infected and non-infected groups, nor even into allergic and non-allergic groups.

When patients with purulent sputum were compared with other asthmatic patients, no significant differences were found in the frequency of extrinsic allergens as determined by history, in the incidence of positive family histories of allergy, in the age groups represented, or in the duration of the disease. It was also held that bacterial bronchitis not infrequently has a beneficial effect on asthma by reason of its acting as a "stress factor," and that effective antibiotic therapy of a bacterial purulent bronchitis in asthma sufferers may cause a severe exacerbation of the asthma. The reviewer must interject that, in his experience, these last two clinical observations must be exceedingly uncommon.

According to Fulton and McKinlay,[113] infection with the Friedländer bacillus *(Bacillus mucosus capsulatus* or *Klebsiella pneumoniae)* may be responsible for asthmatic syndromes. In addition to causing fulminating pneumonia and rare cases of meningitis, peritonitis or urinary tract infections, this pathogen seems capable of persisting as a low grade, chronic invader of the bronchi and paranasal sinuses. Of eight proved cases, three had bronchial asthma with bronchitis, three had chronic bronchitis, and one each had bronchiectasis and lung abscess. The patients with asthma were helped by antibiotics selected on the basis of bacterial sensitivity tests: streptomycin and chloramphenicol in two cases, and streptomycin and Terramycin in one case. All were much benefited, one being freed from asthma for two years, though a perennial allergic rhinitis persisted. Of the antimicrobial agents, the most consistently effective was chloramphenicol and its exhibition was held justifiable, when indicated, despite its potential dangers. Among the leads suggesting a persistent search for the Friedländer bacillus were a history of unsuccessful penicillin therapy and the peculiarly green, putrefactive sputum, sometimes becoming yellowish under antibiotic therapy. The bacillus is often confused culturally with *Aerobacter aerogenes* and sometimes dismissed by the laboratory as a trivial contaminant.

Kaplan et al[178] noted that serologic reactions to C-reactive protein have been used as an indication of rheumatic activity and anti-streptolysin O antibody as evidence of infection with Lancefield's group A hemolytic streptococcus. Applied to a series of asthmatic patients, the anti-streptolysin O titres were so scattered as not to be useful. But a proportion of cases classified by the usual clinical criteria as infectious asthma with recent upper respiratory infection showed a significant incidence of positive C-reactive protein determinations, while the atopic group gave none. This test may therefore be helpful as a possible evidence of an allergic infectious factor in asthma. Further studies are under way.

Drugs.—Blamoutier[30] directed attention to the risks of using acetylsalicylic acid (aspirin) in cases of asthma. Though the drug sometimes relieves mild attacks, it can occasionally cause severe paroxysms with typical symptoms. Eleven cases were observed, two resulting fatally. Some had a long history of asthma, while in others the disease did not start until after the drug was first taken. Allergy to aspirin may develop suddenly after years of use, sometimes even with previous benefit to the asthma. The dose responsible varied widely from a few centigrams to many grams. All intradermal and passive transfer tests with aspirin were negative. Accordingly, the drug is considered a hapten. For some reason, aspirin allergy occurs more frequently in females. Any age group may be affected. Previous estimates of aspirin sensitivity in asthma sufferers varied from 0.2 to 10 per cent. Caution in the administration of aspirin to a "new" asthmatic

patient is enjoined. In an article which is essentially a reply to Blamoutier, Albeaux-Fernet and Tardif[3] defend the use of aspirin in asthma. With considerable justification, they declare that if every drug which had ever produced a pathologic reaction in a case of asthma were to be removed from the therapeutic armamentarium, there would be very little left with which to treat patients. In many years of the practice of allergy, they have seen mild or moderate exacerbations result from aspirin in 4 or 5 per cent of their asthmatic cases; however, serious paroxysms occurred in only four cases out of several thousand. Other authorities are cited to show that this occurs in only a trivial proportion of cases. The best test is to have the patient hold a suspension of the drug in his mouth for a few minutes. If the dyspnea does not increase within five minutes, the drug may be administered. The "magnificent" effect of aspirin in asthma may be the result of its stimulating effect on the adrenal cortex.

Brown[39] considered the problems of drug allergy in an article which should be read by every one interested in this subject. He points out that pharmacologic effects and toxic and allergic reactions are all inextricably intertwined. Infinitesimal quantities may be involved, as exemplified by a constitutional reaction subsequent to a skin test by the pressure puncture method using a solution containing 0.001 mg of active protein. After absorption of only part of the test drop and almost incalculable dilution in the blood stream, a bronchospasm may ensue involving over 1,000 square feet of pulmonary tissue. A comparison to a chain reaction is apt.

Bronchial asthma and herpes simplex complicated the streptomycin therapy of pulmonary tuberculosis in two cases as reported by Mechetti.[221] These appeared after three to six days of treatment, and gradually subsided when the drug was discontinued. One patient had previously tolerated streptomycin, and a subsequent course was without incident.

Cibalgine® (a combination of diallylbarbituric acid and aminopyrine) given for headaches was responsible for severe paroxysms and almost fatal episodes of status asthmaticus in a patient observed by Prickman and Peters.[259] When the drug was stopped, the patient's asthma became very much milder.

Hale[143] reported a case of asthma due to the intranasal administration of posterior pituitary powder. After using the preparation daily for ten years for the treatment of diabetes insipidus (and three years after the onset of asthmatic symptoms which seemed to be associated with "colds" and with winter weather), the patient began to associate the paroxysms with the inhalation of the powder. While the attacks were delayed at first, the interval became progressively shorter. Positive skin and passive transfer tests were elicited with extracts of defatted commercial posterior pituitary powder, and with anterior and posterior beef, pork, and human pituitary. When the therapy was changed to injections of pitressin tannate in oil, asthma no longer occurred, although there were occasional transient local reactions.

Many physicians and parents will be interested in the statement[263] that the Salk poliomyelitis vaccine has produced no untoward effects even in children with a history of penicillin sensitivity. Penicillin is present in the vaccine in a concentration less than 500 units per ml. Further experience will indicate whether this will be a problem when the vaccine is used more extensively. The reviewer must speculate whether subsequent booster doses will reveal sensitization to the protein of monkey kidney on which the virus is cultured.

PSYCHOSOMATIC FACTORS

Flanders Dunbar[75] in a new edition of the classic *Emotions and Bodily Changes* has added extensively to the chapter on asthma. Although none of the references are more recent than 1952, it represents a fine compendium of the psychic background of asthma.

Every allergist should be prepared to give his patients expert psychotherapy along with allergic therapy, according to Kaufman.[181] He points out that both allergenic and psychogenic reactions may affect roughly the same final common pathway of the tissues of the shock organ. However, when apparently "allergic" symptoms develop upon exposure to a conditioned psychic stimulus, there is actually a simultaneous background of a low grade or even subclinical allergic reaction. The principal allergic reactions which seem capable of being conditioned are nasal congestion, urticaria, bronchial asthma, and gastrointestinal allergies. All anti-allergic therapy is said to be in part suggestion therapy. Illustrative cases of asthma and other allergic states are reported.

Leigh[198] contributed a critical review of the evidence for psychic factors in asthma. Although written by a psychiatrist, it takes psychiatry to task for employing non-objective approaches and for reporting inadequate studies. "Few physicians concerned with the treatment of asthma would deny that emotional disturbance is in some way related to some attacks, in some patients. . . However, clarity ends and the dilemma begins, for psychiatry enters the lists. Difficulties of language, of methodology, extravagant claims and the prejudices aroused in so many physicians by the word 'psychiatry' all contribute to the confusion. What is the physician to believe—that an asthmatic attack represents a cry of longing for the mother, or simulates an orgasm, or results from repressed hostility? Is he to refer all his asthmatics to a psychiatrist, or employ a psychologist in his clinic, or himself undertake some training, and become a 'psychosomatic' physician?" The psychiatric literature fails to provide the answers. No satisfactory information was found on the psychiatric symptoms of asthmatic patients, although they tend to show signs of neurosis, to be of "compulsive" type, and, during attacks, to manifest depression almost always. Despite many attempts, no particular personality type has been delineated in asthma; Leigh believes that no such type exists. More extensive employment of psychologic techniques and study of genetic psychiatric factors may cast light on this problem.

Regarding the precipitation of attacks, Leigh takes the broad viewpoint that in any one patient various emotions, just as infectious and allergic factors, may cause attacks. There exists no conclusive evidence regarding an interrelationship between psychosis and asthma, nor electroencephalographic abnormalities in asthma. The formulation of French and Alexander (1941) regarding the psychodynamics of asthma and so widely quoted is critically analyzed and is termed "thoughtful and stimulating, but the material presented and the conclusions derived from this material are unsatisfactory to a degree." The hypothesis is neither confirmed nor denied. The therapeutic claims for the psychotherapy of asthma are criticized, particularly for too brief periods of observation, lack of controls, and failure to use statistical methods. "In spite of all that has been written there is no convincing proof that the psychiatric treatment of asthmatics is in any way more productive of better results than any other method."

Leigh concludes, "Whilst it is clear that the psychiatric aspects of asthma have attracted considerable attention, there yet exists no satisfying authoritative paper on the subject. Speculation is rife and is nowhere substantiated by scientific study. . . The need . . . is for the initiation of a long-term (five, ten and fifteen years) project, using adequate control material, and methods subject to statistical analysis. What has already appeared in the psychiatric literature is stimulating, and fertile in ideas, but requires the test of experiment, of confirmation, and of time. Genetic psychiatric studies, and more research into psychophysical relationships in asthma are particularly needed. . . In spite of confident statements to the contrary, no specific psychological constellation has been proved to exist in asthmatics. It appears rather that the asthmatic attack may result from stimuli of varied provenance playing on an organism which is genetically and constitutionally 'predisposed' toward such manifestations. To postulate a common personality and a common basic problem, is in this reviewer's opinion, quite contrary to the observable facts."

Langeveld[104] also accepts the importance of a large psychologic interplay in asthma, but considers highly improbable the supposed relationship between the asthmatic attack as a suppressed cry for help and the cry of the newly-born at the moment of separation from the mother. "Too much stress has been laid on the psychological interpretation of allergy on a libido-genetic mechanism, whereas too little attention has been paid to the fact that the asthmatic with his specific somatic proprioception has the task of finding a 'modus vivendi.'" If, according to the psychoanalytic school, the *loss* of maternal love is assumed to be a causative factor, the benefits of placing a child in an asthmatic care center, day nursery, or the like, can be explained only if separation from the mother is beneficial. Huët's[164] statistics at such a center in Holland illustrate this. Of 187 asthmatic children observed for six months or more, eighty-two were completely asymptomatic after admission to the home, while 105 were unchanged. A positive family history and an earlier onset of asthma occurred with greater frequency in the latter group. While twenty-four cases of the entire series had experienced a violent emotion shortly before the appearance of asthma, and while a purely psychosomatic form of asthma is apparently possible, it is relatively infrequent, occurring in 0.5 to 3 per cent of the total group.

Abramson[1] maintained that the psychodynamic formulation of maternal rejection so often cited as intensifying or even primarily inducing allergic symptoms is frequently not only incomplete but may be misleading in understanding the allergic responses of children and adults. The opposite may occur: mutual engulfment (introjection) rather than parental rejection. Rejection may then ensue when the mutual engulfment fails to satisfy the parental needs. The rejecting parent shows guilt when the child is in danger symbolically. The engulfing parent demands narcissistic satisfaction regardless of any danger to the child. The concept of maternal rejection is difficult to use in brief psychotherapy.

The relative degree to which psychologic factors influence the frequency and severity of asthmatic episodes in children varies widely, according to Bakwin.[13] A number of relationships may be recognized: (1) Any circumstance which makes the child anxious and unhappy may intensify allergic symptoms; these include a "bossy" or dominating mother most frequently, but also difficulties in school and sibling rivalry. (2) The child is aware of the agitation produced by the attacks, and consciously or un-

consciously employs them to obtain his ends or evade responsibility. (3) Emotional tensions may be increased by a sense of guilt in not carrying out instructions, and parents may feel the same. (4) There is fear of an attack, and anxiety in seeing the parents disturbed and worried. Recommended limitation of activities or choice of foods contributes to the emotional tension. (5) Since the child is chronically ill, the bond between mother and child is strengthened, so that the mother becomes even more overprotective.

The child whose asthma has a large psychic component is submissive, immature, irritable, fearful, overanxious and lacking in self-confidence. Other prevalent character traits include overconscientiousness, demanding behavior, striving for recognition, insecurity, and passive dependence. The management involves discussions with the mother, arranging a realistic schedule for the child, making necessary compromises, encouraging the free expression of feelings (ventilation), and avoiding a critical attitude while suggesting errors in child rearing. This can best be done by the allergist, except when the anxiety, dependence and rejection are overwhelming, when psychiatric referral is needed.

Israël[169] submitted thirty adults with asthma to Rorschach testing, showing that as a group they are restricted in their responses, more so than normal controls or even a matching group of neurotics. The impairment was greater in females than in males. The findings correspond with the clinical observation that asthmatic patients are inhibited in their mode of expression. However, it cannot be suggested that the restricted number of Rorschach responses is specific for asthma.

Psychic observations in two cases may be mentioned. Scheflen[304] reported on an asthmatic adult with deficient intelligence and a catatonic type of schizophrenia, who was extremely dependent and had an intense transference to the physician. When rejected by the latter, she cried with expiratory screams exactly like an infant and then had a classic paroxysm of asthma. This promptly disappeared later, when she began to sob and shed tears. Subsequently, in a similar situation, the sequence was repeated. Miller and Baruch[228] described a three-year-old child who had numerous positive skin reactions but whose asthmatic attacks did not correlate in any way with exposure to pollens, with his diet, or with weather or other environmental physical variables. By play psychotherapy with the patient and psychoanalytically oriented psychotherapy with each parent, it became clear that emotional interplay could be correlated with the attacks. Asthma resulted when the child felt he was not loved and when his anger at his parents was blocked from expression by fear. When his anger was expressed, the asthma aborted or cleared.

Ross et al[294] uncovered a large psychoneurotic component in the chronic respiratory disorders of coal miners, including six cases of asthma and an equal number of cases of emphysema. Friedman and his coworkers[108] argued that this is not typical of these workers as a class. In their experience, the incidence of asthma in miners does not exceed 2 per cent. In coal workers with respiratory complaints, psychogenic disturbances occurred in 15.7 per cent, less than in the general population.

In a co-ordinated psychiatric, clinical, and biochemical study, Knapp and Michelson[184] found a wide range of personality disturbances in asthmatic subjects and a reduced urinary steroid output as compared with a control group. Marked fluctuations occurred in the steroid excretion measured at weekly intervals. It appeared to fall following exacerbations of the illness,

whereas at the onset of the asthma there were often sudden rises in the output occurring at times of emotional turmoil and widespread personality disturbance.

A combination of ACTH and psychotherapy was found by Groen[138] to be beneficial in asthma. Although showing considerable variation, asthmatics have certain personality traits in common: marked egocentricity, an infantile form of stubbornness sometimes with self-deceit, a tendency toward domination and tyranny, a reduced capacity for adaptation to disagreeable situations, impatience and a tendency to impulsive behavior, emotional hypersensitivity often combined with disregard for the feelings of others, a marked need for love and affection (sometimes masked), an attitude of rivalry or jealousy, an ambivalent attitude toward authoritative figures, and difficulty in solving interpersonal conflicts. Psychotherapy by means of psychoanalysis, "progressive relaxation," psychiatric interviews or group discussions, was helpful. However, the results were transitory in many cases and were less favorable in adults than in children. Accordingly, advantage was taken of the euphoria-producing effect of corticotropin, employing a small dosage in conjunction with psychotherapy, and avoiding subsequent relapse when the drug was discontinued. The results of combined ACTH therapy and group psychotherapy in ten cases was better than in patients treated symptomatically (epinephrine, aminophylline, antibiotics and respiratory exercises), or with the same modalities plus ACTH, or with symptomatic measures plus psychotherapy. The average daily dose of corticotropin was 15 to 20 mg early in the study but was later reduced to 5 to 10 mg. It was noted that the patients became dependent on the group for psychic support. Although the series is small, further investigation of this combined technique is suggested.

EXPERIMENTAL ASTHMA AND INDUCED ATTACKS

Herxheimer[155] found that a 1 per cent aerosol of 5-hydroxytryptamine (serotonin) caused severe bronchospasm and subsequent convulsions in guinea pigs. The symptoms were not antagonized by mepyramine (Neoantergan®) but partly so by atropine. In normal subjects, a 0.67 per cent aerosol for sixty seconds had no effect on the vital capacity or expiratory velocity. In half of a group of asthmatic patients, the same exposure produced pronounced asthmatic attacks which subsided spontaneously or were abolished by isopropylarterenol aerosol. In two of three patients who had been asthma-free for a long time, there resulted a mild reduction in vital capacity and expiratory velocity. The actions of the drug were considered similar to those of histamine and acetylcholine, readily provoking broncho-obstructor effects in the asthmatic patient.

Swineford[336] has extended his studies on bacterial haptens, employing pneumococcal polysaccharides for aerosol desensitization of guinea pigs passively sensitized with specific heterologous (rabbit) antiserum. Aerosols of the specific hapten elicited respiratory distress of varying intensity from slight dyspnea to typical anaphylactic death in the sensitized animals. Reactions to inhaled hapten may differ from those to intravenous hapten since the latter may still produce anaphylactic death after a negative reaction to the aerosol. Desensitization could be readily produced by specific hapten aerosols in minutes, and such desensitization may last at least nine days. Local desensitization by a weak but effective concentration of aerosol could protect against five to fifteen multiples of that concentration. Two patterns of aerosol desensitization were noted: (1) after several successive de-

creasingly severe respiratory reactions; and (2) recovery from respiratory distress while still in the aerosol. These experiments were done with type VI pneumococcal polysaccharide; for some unexplained reason, type II antisera and polysaccharides failed to sensitize the animals. The polysaccharides are here considered to be haptens, since they do not sensitize guinea pigs, although, under proper conditions, they may be antigenic in man and in rabbits. There is need to investigate the whole problem of local *vs.* systemic desensitization, and the possible employment of haptens for desensitization.

According to Gross[139] typical asthmatic crises could be produced in the castrated white male rat by the intraperitoneal injection of ovalbumin, but only provided a pre-existing bronchial irritation had been produced. The last was accomplished by a previous aerosol of dilute acetic acid. The same results could be obtained in the intact female rat, but less regularly, and not at all in the intact male rat. It was concluded that a local pulmonary irritation is a necessary factor in the production of experimental asthma in the rat and that some factor of sex hormones plays a part. The same author had previously reported similar observations with regard to histamine aerosol following an aerosol of acetic acid.

Rebhun and Feinberg[276,277] studied the fate of epinephrine and the effect of sympathomimetic amines, amine oxidase inhibitors, and enzyme blocking agents on asthma in the guinea pig induced by antigen or histamine aerosols. The fate of epinephrine *in vivo* is still obscure. The enzyme, amine oxidase, is thought to account for about half of the degradation of epinephrine in the body. Amine oxidase has been shown to be inhibited by certain amines, particularly Marsilid® (iproniazid or 1-isonicotinyl-2-isopropyl hydrazine). In the passively sensitized guinea pig challenged with an aerosol of ovalbumin, epinephrine had a protective effect when administered in optimal doses, the animal showing milder reactions and tolerating a longer exposure to the ovalbumin aerosol than the unprotected group. The larger doses seemed to give greater protection. Administration by continuous infusion seemed more efficacious and less dangerous than when the epinephrine was given in a single injection. The administration of Marsilid or its addition to the dose of epinephrine was without protective effect on the induced asthma, and the same was true in anaphylactic experiments. It can be postulated that there must be other mechanisms of epinephrine inactivation in the body, perhaps by enzymes other than the amine oxidase or by conjugation. It is also possible that Marsilid inhibits histaminase even more strongly than it inhibits amine oxidase, thus unfavorably affecting the enzymatic balance.

In further experiments, they[277] incorporated observations with two other antituberculous drugs known to block enzyme activity: isoniazid (Rimifon or isonicotinic acid hydrazide) and pyruvic acid isonicotinoyl hydrazone; also with sympathomimetic amines, including phenylethylamine, tyramine, and amylamine. Monoamine oxidase destroys sympathomimetic amines, such as epinephrine and phenylethylamine (but not ephedrine). Diamine oxidase inactivates histamine, among other substrates. The inhibition of monoamine oxidase by iproniazid, thus making more exogenous or endogenous epinephrine available, did not influence the guinea pig asthma produced by a histamine aerosol. Likewise, the inhibition of diamine oxidase (histaminase) by isoniazid, thus making more exogenous or endogenous histamine available, did not increase the asthma produced by a histamine aerosol. The drug pyruvic acid isonicotinoyl hydrazone, which has little

inhibiting action on either monoamine or diamine oxidase, increased the tolerance of the animals to the histamine aerosol. The mechanism is unexplained. The amines, phenylethylamine, amylamine, and tyramine, had no influence on asthma produced by aerosols of histamine or antigen. The pretreatment of the animal with iproniazid, which inhibits the action of monoamine oxidase, did not affect the influence of the asthma-producing aerosols; nor did it enhance the protection produced by intraperitoneal injection of ephedrine. Although Benadryl® is a moderate inhibitor of monoamine oxidase, the addition of iproniazid failed to potentiate its action in preventing histamine-induced asthma. It is concluded that the action of monoamine oxidase cannot be the only mechanism in the prevention of anaphylaxis in the guinea pig, that the antiallergic action of Benadryl does not depend on monoamine oxidase, and that the rôle of endogenous diamine oxidase (histaminase) in the regulation of histamine shock in the guinea pig is negligible.

Winter and Flataker[376] devised a technique permitting objective and quantitative measurements of the cough response of a sensitized guinea pig, and so differing from the previous methods employed by Feinberg and by Herxheimer. The guinea pigs, passively sensitized by the intravenous injection of known amounts of specific rabbit antiserum containing a determined antibody nitrogen content, were exposed to aerosols of the specific antigen ranging from 0.1 to 8.1 per cent for a period of ten minutes, and the number of coughs induced was recorded semi-automatically. Some dyspnea also occurred, but severe anaphylactic shock seldom appeared under these conditions. The antigen, both for the immunization of the rabbits and the aerosol challenge, was crystalline bovine plasma albumin. The number of coughs induced bore a relation, within a limited range, to the amount of antibody administered and to some extent to the concentration of antigen. The cough so produced was controlled by pretreatment of the animal by the antihistamine pyrilamine maleate (Neoantergan®) or by cortisone, but not by codeine or propadrine. The last two drugs were effective against the irritative cough produced by ammonia fumes or aerosolized dilute acid, while pyrilamine and cortisone were not. Only the antitussive, narcotine, which is not antihistaminic, effectively controlled both types of cough. A degree of synergism between pyrilamine and cortisone was observed in the sensitized animals.

PULMONARY FUNCTION TESTS AND RESPIRATORY PHYSIOLOGY

The respiratory physiology of asthma, emphysema and respiratory acidosis has been accorded much attention in the past year. Much of it is difficult to evaluate briefly.

Guerrant[140] summarized the mechanics leading to, and the effect of, poor ventilation in asthma. The airway obstruction causes (1) a slow flow rate, leading to reduced maximum breathing capacity; (2) increased respiratory effort, leading to a high intra-thoracic pressure; and (3) overdistended lungs, leading to a reduced vital capacity, increased residual volume, increased total capacity, poor lung mixing, and poor respiratory mechanics. All these factors combine to produce poor ventilation, resulting in reduced alveolar oxygen and unsaturated arterial blood, and perhaps an increase in alveolar carbon dioxide with respiratory acidosis.

Riley[281] emphasized the importance of the work of breathing in relation to respiratory acidosis. Pulmonary ventilation determines the partial pressure of carbon dioxide (P_{CO_2}) in the alveolar gas, and through it, the

arterial P_{CO_2}. When the latter is higher than the normal value of approximately 40 mm Hg, respiratory acidosis is present. Calculations of the oxygen consumption available for nonventilatory work (beyond that needed for the work of breathing plus basal metabolism) shows that in a normal subject the amount rises rapidly with increased alveolar ventilation; but in a patient with severely obstructed breathing, the curve begins to fall rapidly with the higher levels of alveolar ventilation. A point is reached, when the patient's pulmonary ventilation approaches his maximum, where no oxygen at all is available for nonventilatory work because it is all used up in the act of maintaining the high respiratory volume. However, the physiologic interrelationships are such that, at a given level of ventilation, more oxygen is available when the alveolar P_{CO_2} is at a higher level. In other words, under these circumstances, the patient breathes less for a given amount of total oxygen consumption, and more remains for nonventilatory work.

In this light, an increase in alveolar P_{CO_2} or respiratory acidosis occurs as an adaptation to an undesirable physiologic circumstance, the difficult breathing. There are clear therapeutic implications in this concept of respiratory acidosis. Since an increase in the work of breathing is the primary cause of the trouble, its reduction must be the primary aim of therapy. Thus, bronchodilators reduce the resistance to the flow of air, antibiotics control inflammatory swelling, expectorants and steam and liquefying agents help in the removal of secretions, steroids reduce spastic narrowing of the airways by controlling allergic manifestations, breathing exercises may reduce the oxygen cost of breathing by permitting more efficient use of the muscles of respiration, respirators and other mechanical devices help in carrying nebulized bronchodilators deep into the lungs, in sustaining ventilatory volume and in raising secretions, and rest is a means of reducing the work of breathing. To the extent that breathing can be made easier, respiratory acidosis is a treatable condition.

Much of this thinking is reflected in an Editorial.[196] In the common forms of dyspnea, as in emphysema, breathing is in fact harder work; but the capacity for respiratory work is often impaired as well. In emphysema, the force that can be applied to the lungs often falls off quickly with movement and this is one of the factors limiting vital capacity and maximum respiratory work. Accordingly, the patient must have his effort assessed in relation to his own possible maximum. Dyspnea in organic disease can therefore be taken as reflecting an increased excitation of the respiratory center. whether or not this results in greater expiratory work, and whether or not the greater work results in greater ventilation. Westlake[373] pointed out that acute respiratory failure may be precipitated by chest infections in patients whose alveolar and arterial carbon dioxide tensions are within normal limits when they are well. The paradox of hypoventilation in the face of anoxemia and hypercapnia is most likely to happen with subjects suffering from chronic bronchitis or emphysema.

Schiller and Lowell[305] reviewed the recent literature on pulmonary function testing in asthma and added their own observations. Asthma causes alterations in the lung volume and its subdivisions, faulty distribution and "mixing" of the inspired air, and a consequent impairment in the exchange of lung and blood gases. Most previous studies on asthma have been done during remissions so that striking changes were rarely noted. In asthma, the vital capacity, the expiratory reserve volume and especially the inspiratory capacity are decreased. If emphysema is also present, significant-

ly larger volumes are often produced if the vital capacity and expiratory reserve volume determinations are performed slowly, since poorly ventilated areas then have sufficient time to empty. The residual volume and functional residual capacity (which cannot be determined from a spirogram) are markedly increased during paroxysms, but may be within normal limits, even when other abnormalities of pulmonary function are present, when the asthmatic patient is comparatively free of symptoms. Determinations of total lung volume, because of its wide variability, and of minute volume are of little value in estimating ventilatory impairment in asthma. The maximum breathing capacity is often reduced out of proportion to the vital capacity. The more complex methods of assessing the evenness of distribution of inspired gas within the lung (intrapulmonary mixing) and of measuring the volume of the so-called "poorly ventilated space" indicate considerable impairment in asthma and even more so in emphysema. There is no evidence for impairment of the diffusing capacity in asthma. Other studies often required include arterial blood gases and pH, the ventilation equivalent, and the rate at which arterial oxygen saturation rises upon the inhalation of oxygen.

During induced asthmatic attacks, there is a decrease in the vital capacity and its fractions, an increase in functional residual capacity, and sometimes also a fall in arterial oxygen saturation or a prolongation in the resaturation rate. All these may be quickly reversed, in whole or in part, by bronchodilator drugs. In severe attacks, a reduction in minute volume may occur, to be followed shortly by an increase beyond the initial level. Various types of "open" and "closed" systems may be used; each has its advantages and disadvantages. The maximum breathing capacity is not well adapted for asthmatic patients, and a kymographic record of a maximal expiratory effort is more suitable. To determine intrapulmonary mixing and residual volume, Schiller and Lowell prefer the helium dilution method.

Seabury[309] has made a praiseworthy attempt to simplify and reduce the apparatus, time, and personnel required for reasonable pulmonary function testing in the office practice of allergy. While no substitute for pulmonary auscultation and fluoroscopic examination, the method advocated supplies a permanent, graphic and quantitative record. It is thus possible to follow the patient's clinical course, to detect pulmonary emphysema, and to evaluate therapy on either an acute or chronic basis. This simplified approach will enable the allergist to determine (1) the degree of ventilatory impairment, (2) the relative amount of unrelievable expiratory trapping, (3) the difference between primarily obstructive impairment and primarily restrictive dysfunction, and (4) the breathing disability after maximum bronchodilatation. To accomplish this requires only a 13.5 liter Collins respirometer (which can also be used for basal metabolic rate determinations) and a Segal-Herschfus vital capacity timed interval ruler. Records are made of ordinary and deep breathing, and of the timed vital capacity. In addition to the three-second expiratory volume, the total vital capacity and the time required for vital capacity, study of the shape of the tracing reveals expiratory prolongation and retardation, or inspiratory prolongation or restriction. These findings are probably more valuable than the maximum breathing capacity in asthmatic patients. The records are repeated after effective bronchodilatation. Serial records are of great value as an index of the progression or control of the disease, to detect and follow emphysema, and to suggest possible complications.

The intensive studies of Motley[238-241] have also shown that spirogram tracings of the three-second timed vital capacity, in conjunction with the maximum breathing capacity, are useful screening tests to detect early lung function abnormalities even before subjective or roentgenologic changes are apparent. A more accurate evaluation also requires total vital capacity, the shape of the exhalation curve, the degree of bronchospasm, the residual volume and alveolar nitrogen content after oxygen breathing, the arterial oxygen saturation at rest and after exercise, the oxygen uptake during exercise, and the character and duration of dyspnea after exercise. Bronchospasm is estimated by repeating the spirographic tracing at least ten minutes after administering a bronchodilator. A numerical Ventilation Factor has been devised to provide a single figure of the patient's ability to use the chest and lungs as a bellows for aerating the alveoli. It is derived as the numerical average of (1) the three-second vital capacity as per cent of normal predicted, (2) the maximal breathing capacity as per cent of normal predicted, and

$$(3)\ \frac{\text{normal residual percent of total lung volume}}{\text{observed residual per cent of total lung volume}} \times 100.$$

The vital capacity as a single measure of lung function can be misleading and responsible for false interpretations.

Fry et al[111] found the pressure-flow curves of patients with pulmonary emphysema to be abnormal. Resistance to gas flow is markedly increased, both to laminar gas flow and as a result of eddying turbulence. The latter increases progressively as the rate of gas flow increases.

None of the several methods for the study of respiratory air flow is entirely satisfactory, especially in children, according to Rapaport and his co-workers.[273] They therefore recommend the electrical pneumotachograph which, in conjunction with an oral-nasal mask, provides instantaneous recording of the rate of change in the ventilation of the lungs. Preliminary studies, mostly on asthmatic children, proved the method to be promising. It may be of value in the differential diagnosis of cases with repeated episodes of pulmonary infection accompanied by wheezing, and in the prognosis of asthma to determine if resistance factors may be reversible. The prognosis seems to be better in those children giving normal curves between asthmatic episodes than in those whose curves remain unchanged. Huët[163] observed that in asthmatic children the residual air tended to become relatively less and the vital capacity relatively greater as the child grew older, especially in the milder forms of asthma; the condition improved spontaneously with increasing age in these children in an asthma treatment center.

DIAGNOSIS

Among others, Sutherland[332] and Squier[326] have discussed the diagnostic work-up of asthmatic patients.

The employment of skin testing to determine the causal allergens in asthma as well as in other allergic states has been critically evaluated by several authors. Peshkin[256] emphasized the pitfalls and limitations of the method. The lack of uniformity of preparation and standardization of test allergens in the hands of commercial and individual laboratories constitutes a pressing problem. Where a single patient suffers from asthma and some

other form of allergy such as eczema, urticaria or angioneurotic edema, a reacting substance may relate only to the nonasthmatic syndrome. Thus, about one-half of the egg and fish allergizations which he found in asthmatic children were responsible only for cutaneous and digestive manifestations. An Editorial[83] reiterated the accepted viewpoint that skin tests are of diagnostic value only if interpreted in the light of the clinical findings.

The inconstancy of skin test reactions in the same patient was noted by Ogilvie,[249] Herxheimer et al,[157] Tuft and Heck,[349] and Matheson.[213] Ogilvie repeated intradermal skin testing to the common inhalant allergens in 209 cases of asthma after a period of two to seventeen years (average, seven years). Only thirty-one of the patients were under fifteen years of age. The results were found to have altered widely or significantly in ninety of the cases: in forty cases, some previously positive tests became negative; in fifty, the opposite occurred; while in five, there were changes "in both directions," and in 114 cases, no significant changes in the test pattern. The change or lack of it showed little or no correlation with the clinical progress of the patients, most of whom were improved, although fifty-five cases were unimproved, and sixteen were worse. It was concluded that repeated skin testing seems an unreliable indication of the clinical course and is of little or no prognostic value in asthma. Employing the prick test with relatively concentrated extracts of twelve inhalant allergens including pollens and mixed molds, Herxheimer et al[157] found that repetition of the testing on different days or at different times of the year gave exactly the same results in only three of twenty-one patients. In the other eighteen cases there was considerable variation, one or several of the reactions which were positive at first becoming negative in the subsequent test or *vice versa*. Sometimes late reactions were replaced by immediate reactions. Although not dealing exclusively with asthma, Tuft and Heck[349] studied the changes in test reactions in a series of their own patients and by means of a questionnaire to allergists. It was determined that sensitization may be acquired to new food allergens, especially foods commonly eaten. Once skin sensitization occurs, it changes very little as the result of allergen avoidance or of treatment. Specific pollen therapy (unless long-continued) and avoidance of foods for varying periods of time as a rule produced little or no significant change. A reduction in skin test reactions is in itself not a criterion of improved tolerance indicating the readdition of a food or the cessation of pollen therapy. Skin test reactivity may diminish with advancing age, especially after the age of fifty years. However, in children, Matheson[213] found that while positive reactions to inhalants rarely became negative, those to foods could become negative after elimination of the allergenic food.

Herxheimer and his coworkers[157] evaluated the prick test with twelve inhalant allergens in 300 patients with respiratory allergy, of whom more than half suffered from asthma, and in 100 normal subjects. In 95 per cent of the patients and in 51 per cent of the controls, one or more skin reactions were positive. Only two of the thirteen with negative skin reactions were typical asthmatic patients with a long history. Bronchospasm had been preceded by bronchitis in nine of them. The high incidence of positive reactions in normal subjects limits their value in the diagnosis of respiratory allergic disease. Their absence makes allergic disease unlikely, although it does not absolutely exclude it. In a considerable proportion of the patients the results of the skin tests did not correlate with the clinical evidence. Thus, in six patients negative reactions occurred with the specific

allergen clearly incriminated on clinical grounds. In another group of forty-five patients, at least one skin reaction correlated with the clinical evidence, but there were also one or more additional positive skin reactions at variance with the clinical picture. On the other hand, seventy-one bronchial (aerosol) tests in fifty-two patients gave reactions which were always compatible with the clinical evidence. In about two-thirds of the trials, the bronchial test and the skin test were both positive to the same allergen, but discrepancies occurred in the remainder. Late skin test reactions were not infrequent and where a positive skin test agreed with the clinical evidence or the bronchial reaction, the skin reaction was often a late one. Apparently those reactions which are repeatedly positive or negative, and late reactions, may be given more credence. It is concluded that skin tests may possess some limited value for the identification of a causative allergen if no other evidence of specific allergy is present, and may give some guidance for the direct testing of the respiratory shock organ. Skin testing should be limited to cases in which it is suspected that the symptoms are due to nonallergic causes or in which precise clinical evidence of a specific allergen is lacking in an undoubted allergic disorder.

Salén and Björnsterna[296] studied the risks of intracutaneous testing. Of 1,000 cases, chiefly of asthma, submitted to tests with thirty to forty extracts at one sitting, shock-like reactions were observed in 1.1 per cent. One medical student with polyvalent asthma, who had shown only a very slight reaction to horse dander ten years before, was found dead shortly after performing a cutaneous test on himself with a freshly prepared extract. The literature is said to contain fourteen instances of fatal reactions due to skin testing.

An argument in favor of the passive transfer (Prausnitz-Küstner) method of testing of asthmatic patients was presented by Taub and Rosenberg.[342] This method is claimed to give information which sometimes cannot be elicited by direct skin testing. Antihistaminic drugs or epinephrine may interfere with the response to the latter. In one illustrative case, a patient eighteen years of age, the discovery of sensitivity to yeast, tomatoes, feathers and molds was made only after indirect testing, and was the turning point of the case. The patient had received epinephrine in oil at least once daily during the earlier routine skin testing.

Ancona and Schumacher[4] claimed that raw foods reduced to a paste or powder and then frozen were superior for scratch testing to commercial extracts employed by either the scratch or intradermal techniques. Storage in the frozen state for periods up to four years did not affect the antigenic potency of the materials.

Buffum[46] discussed the diagnosis of asthma in infancy. Three criteria should be met: the occurrence of recurrent wheezing, the demonstration of the allergic state, and the absence of any other condition which could cause wheezing. Babies do not always have typical physical findings of asthma. There is sometimes simply noisy, difficult breathing in which the musical expiration is drowned out by the loud gurgling of tracheal mucus. One or more of the following corroborate the allergic state: eczema, allergic rhinitis with eosinophilic discharges, definitely positive skin tests, a demonstrable relation of the asthma to some inhalant or food, and eosinophilia of the bronchial secretions. Evidence in this category is often lacking, most infants with asthma not having eosinophils in the nasal or bronchial exudates, or positive skin tests. Associated evidence which may prove helpful includes a positive family history, a past personal history of colic, vomiting

or pylorospasm, or a blood eosinophilia of 4 per cent or more. Lacking the full picture, it is often necessary to be content with only a tentative conclusion, taking weeks or months to work out a definite diagnosis. Dietary manipulation or symptomatic clearing on admission to a hospital may clarify the point. Definitely positive skin tests are likely to appear during the second or third year of life. Or, even if no other evidence is found, the clinical pattern of repeatedly recurring wheezing justifies the diagnosis. Infant wheezing of purely infectious nature becomes less common as time passes, so that either wheezing ceases to occur or atopic causes become evident. Buffum[45] observed that 19 per cent of a series of cases of asthma, with an onset before thirteen years of age, began in the first year of life. It appeared that asthma beginning in infancy tends to be more severe, that a family history of allergy was lacking in about one-third of the cases, and that food sensitivity occurred more frequently than in later life. The prognosis in these asthmatic infants was much the same as in older children. Clein[53] points out that infant asthma occurs more often as continuous wheezing of mild to severe degree, usually worse at night. Between actual definite asthmatic attacks some wheezing or cough occurs during each day. Many babies have a pre-asthmatic cough which often precedes the typical asthmatic wheeze. They frequently have large amounts of mucus in their throats, especially while eating or with excitement.

Sherman[319] suggested a simple objective screening procedure for the diagnosis of asthma, particularly applicable to the military situation. The subject is given a rapid intravenous injection of 0.03 mg of histamine phosphate (in terms of histamine base) or of 0.5 mg of methacholine chloride. A preceding injection of saline solution constitutes a control. Serial vital capacity determinations are performed one-half and one minute after the injections, and repeated each minute until the value has returned to or near the baseline. The chest is ausculted and the patient questioned regarding subjective symptoms. A reduction of 11 per cent or more in the vital capacity after either histamine or methacholine or both is considered a positive response. Of thirty cases of asthma, seven gave positive responses to histamine, eight to methacholine, and fifteen to both; none was negative. Of eleven nonpulmonary patients, four gave positive responses; of nine control subjects, two were positive. It is concluded that while a positive response does not establish the diagnosis, a negative one helps to rule it out. The results must be evaluated in the light of the entire clinical picture. Cardiac arrhythmia, marked hypertension, or the presence of an asthmatic paroxysm are contraindications to the test. Methacholine caused a brief apnea in two instances and supraventricular tachycardia once, but no other side effects. Histamine produced a shock-like state in one patient; the histamine flush and transient headaches were not a problem. Protection studies employing antihistaminic or anticholinergic drugs, selected according to the subject's response to the tests, are under way.

DIFFERENTIAL DIAGNOSIS

Clerf[54] discussed the differential diagnosis of wheezing respiration. The mechanism of wheezing, in simplified terms, is essentially a partial check-valve obstruction in conjunction with the normal narrowing of the bronchial lumen occurring during expiration. Accordingly, the causes of wheezing are numerous: bronchial asthma, obstructing secretions, benign or malignant neoplasms, cicatricial stenosis, endogenous and exogenous for-

eign bodies, tuberculous tracheobronchitis, and compressive lesions such as substernal goiter, thymic compression and foreign body in the esophagus. Simple thymic enlargement is rarely responsible. Laryngeal lesions may cause stridorous breathing as in congenital laryngeal stridor. In asthma dyspnea is present and is expiratory in time, and wheezing is heard throughout both lungs, while in foreign body or neoplasm, it is louder on the affected side. The adventitious sounds are usually more moist in asthma than in a localized obstructing lesion. The history and the presence of associated allergies or prodromal symptoms are helpful. In bronchiogenic carcinoma, the incidence of wheezing is low, but careful questioning often reveals that a wheeze was present for a short interval early in the course of the disease. Mediastinal lesions producing tracheal and bronchial compressive stenosis, such as aneurysm of the arch of the aorta, Hodgkin's disease, primary lymphoblastoma and mediastinal metastasis, may cause wheezing. In the older age group, cardiac asthma or paroxysmal cardiac dyspnea, advanced pneumoconiosis and pulmonary emphysema must be considered. A superimposed acute bronchitis may induce asthma-like attacks. The history and physical examination, supplemented by roentgenologic studies, will usually lead to a diagnosis. If obstruction exists, bronchoscopy is usually necessary.

In a discussion of asthmatoid syndromes, Derbes[70] presented cases of a pheochromocytoma causing cardiac asthma, fibrocystic disease of the pancreas (mucoviscidosis) which causes some degree of wheezing in almost half the instances, and carcinoma of the lung. Warning signals that wheezing may be of nonasthmatic origin include onset in later life, fever, pain, weight loss, hemoptysis, copious expectoration, and changes in the respiratory pattern or character of the attacks.

Douglass[73] pointed out that the wheeze of tracheal or bronchial obstruction is heard predominantly, and often exclusively, during the inspiratory phase of respiration. This helps to differentiate it from the bronchospasm of asthma in which the wheeze is heard during expiration. To be considered are foreign bodies, neoplasms, broncholithiasis, bronchostenosis (the sputum-retention syndrome), atelectasis, and bronchial obstruction by compression ("the middle lobe syndrome"). All these require bronchoscopic management. Good and Harrington[128] found that bronchial adenomas may exist for long periods of time in an asymptomatic phase before calling attention to themselves by causing hemoptysis or symptoms of bronchial obstruction.

That the clinical differentiation between bronchial and cardiac asthma is often extremely difficult was re-emphasized by Ferris,[93] Gelfand,[122] and Wall.[370] Both are characterized by nocturnal attacks, bronchial constriction, and wheezing. Ferris[93] pointed out that paroxysmal cardiac dyspnea or acute left ventricular failure may or may not be accompanied by bronchial constriction and wheezing; only when these are present should it be called cardiac asthma. The mechanism of the bronchoconstriction in heart failure is not well established. Bronchial reflexes from congested lungs and pulmonary circulation may be possible. Perhaps there is an element of "asthmatic diathesis"—but no real evidence exists. In any event, cardiac asthma appears to be a response to cardiac failure in individuals peculiarly susceptible to bronchoconstriction. The development of asthmatic symptoms in a patient without a history of allergic manifestations should suggest cardiac failure. Congestive râles are usually, but not always, present in cardiac asthma; chest roentgenograms may reveal butterfly hilar congestion or en-

largement of the heart. Both cardiac and bronchial asthma will respond to morphine, epinephrine and aminophylline, but morphine is contraindicated in the bronchial, and epinephrine in the cardiac, forms. Gelfand[122] outlined the hypotheses explaining wheezing in cardiac asthma as (1) congestion or edema of the bronchiolar mucosa, (2) active bronchoconstriction, (3) compression of the bronchioles by congested capillaries, and (4) intrinsic obstruction due to edema fluid in the bronchiolar lumina. In addition, there may be unknown contributory factors. Differentiation from bronchial asthma is made on the basis of the history, including family and past medical history, and the age of the patient; evaluation of cardiac function, including electrocardiographic and roentgen studies; skin tests; laboratory data, particularly the circulation time; pulmonary function studies; and the therapeutic response to various drugs, including Mercuhydrin®. The last has proved of greatest value, especially in the elderly patient. Wall[370] considered the determination of vital capacity, venous pressure, circulation time and blood volume, and chest roentgenograms helpful.

According to Segal et al,[313] bronchospastic crises, resembling paroxysms of bronchial asthma, may occur during certain stages of the course of chronic pulmonary emphysema. The dyspnea in emphysema may be caused by such acts of exertion as coughing, sneezing, or straining, and is accompanied by hyperventilation. There is a tendency for the cough to become more persistent and readily initiated by nonspecific irritants such as cold air, wind, fumes, dust and smoke. Trimble and Crenshaw[347] agreed on the difficulties of differentiating the dyspnea resulting from bronchospasm and bronchiolitis from that resulting from the dissolution and absorption of actual lung structures due to disease affecting the bronchial arteries and causing a type of bullous degeneration.

Ziskind,[381] in reviewing the clinical patterns of bronchitis, pointed out that the persistence of the disease after an acute onset is often the result of underlying hypersensitivity. This opinion may be reached in a given case when the results of antibiotic therapy are poor, when the response to steroids is prompt, and sometimes when a clinical picture of bronchial asthma persists after the infection has subsided. Recurrent localized or nonlocalized bronchopneumonia may complicate a pre-existing asthma. Frequently, infection must be overcome before the allergic state can be effectively managed.

Acute bronchiolitis, also known as capillary bronchitis, occurs in young infants and rarely after two years of age. Traisman and Bigler[345] state that it must be differentiated from asthma, asthmatic bronchitis, laryngotracheo-bronchitis, and bronchopneumonia. Although emphysema is present in both asthma and bronchiolitis, the latter lacks the characteristic prolonged expiration with squeaks and rhonchi. A therapeutic trial of epinephrine gives relief in asthma and often has some effect in asthmatic bronchitis, but none in bronchiolitis. Ephedrine and antihistaminic drugs are also of no value in the last-named condition.

"Farmer's lung" or idiopathic pneumonitis or pneumoconiosis in farmers is sometimes considered to have an allergic component. Study of three cases, however, led Soucheray[324] to the tentative opinion that the disease is a form of bronchopulmonary moniliasis. *Candida albicans* was repeatedly isolated from the sputum of one patient. In each case there was a history of respiratory symptoms on exposure to dust from moldy silage, dyspnea or cough for several months, and improvement on change of environment.

TREATMENT: GENERAL CONSIDERATIONS

The general aspects of the treatment of asthma were discussed by Owen,[252] Vallery-Radot,[364] Lowance,[204] Kovnat,[188] Thomas,[344] Blanton,[31] Guerrant,[141] and Bernstein and Klotz.[26] One must agree with the statement by the last-named that effective treatment for asthma is polyphasic and a wide range of modalities is employed: pharmaceutic, endocrine, antibiotic, psychologic, and physiotherapeutic. "As the fuller picture of the physiology, immunology and pharmacology of asthma comes into focus we once again find ourselves using both drugs and hormones, in addition to the methods of the allergists, in a wide-range attack on this clinical problem." The reviewer should not be considered carping if he comments that he has always been of the opinion that the allergist is a physician engaged in the study and treatment of allergic diseases and has always been free to employ all effective therapeutic methods.

The management of nonallergic bronchial asthma was outlined by Stuppy[331] and Swineford,[339] of status asthmaticus by Talmadge[341] and Carryer and his co-workers,[49] and of asthma due to pollinosis by Forman.[102] The last-named surprisingly approves the inhalation of the smoke from burning stramonium leaves in mild cases.

The extremes of life have not been neglected, Levin[201] and Dees[68] covering the management of asthma in childhood, and Sheldon, Lovell and Mathews[318] and Rosenberg[292] in the aged. It is clear that aside from physiologic and pharmacologic considerations commensurate with age differences, the same principles apply to the treatment of pediatric and geriatric asthma as to any other age group. Likewise, the problems of asthma in the military situation are completely identical to those encountered in civilian practice, according to Radke.[271] On the whole, asthmatic personnel can be successfully utilized in overseas armed forces installations.

Banyai[17] discussed the biomechanics and treatment of cough, particularly emphasizing bronchodilator drugs. He also noted that ethyl alcohol, being an effective relaxant of spastic peribronchial and peribronchiolar smooth muscles, is helpful in some otherwise uncontrollable cases of bronchial asthma, when taken in one of the usual alcoholic beverages. Burnham[48] observed in himself and others that the slow inhalation of the vapors of 70 per cent ethyl alcohol poured on gauze will promptly ameliorate an irritating cough without abolishing the useful cough.

THERAPY: HYPOSENSITIZATION

Assuming that an hereditary background is required for asthma to appear and that hepatic insufficiency is basic to its emergence, Denis[69] still found desensitization indispensable in one-third of his cases. Polydesensitization is preferred, since most asthmatic patients are sensitized to a variety of agents. A rapid and long-lasting cure is claimed in 80 per cent of the patients treated. Comeau[60] usually begins the desensitization of hospitalized asthmatics before their discharge from the hospital, along with intramuscular or intravenous corticotropin in cases of status asthmaticus, and such supportive therapy as may be needed. Epinephrine is rarely used. The duration of morbidity and of hospitalization was reduced by this technique, and fewer relapses occurred. On the whole, excellent results were reported in a two-year follow-up. The principal cause of failure was the patient's unwillingness to continue with the injections because of a false sense of security. Frankland and Augustin[105] reported good or

excellent results from preseasonal therapy with either a crude pollen extract or purified pollen protein in 94 per cent of a series of cases of bronchial asthma due to grass pollen sensitivity. Results were much less favorable with an ultrafiltrate of the crude extract containing the pigments, carbohydrates, amino acids and peptides, and practically inert in skin testing.

Three reports from Scandinavian countries deal with the risks of desensitization, although in all "rush desensitization" was employed with several injections a day at intervals of two to four hours. Bruun[44] noted that five fatalities due to specific anti-allergic treatment occurred in Scandinavia in the last three or four years. In a large series of asthmatic cases, Salén and Björnsterna[296] noted that 44.2 per cent had clinical reactions, usually urticarial and fairly mild, on one or more occasions. However, one thirteen-year-old boy died within fifteen minutes, despite heroic therapy, of a systemic reaction starting about two hours after an injection of 0.6 cc. of a 1:10 dilution of horse dander. He had received treatment for fifteen days and had been given a somewhat smaller injection some hours earlier. Autopsy revealed typical asthmatic changes in the lungs and hepatic congestion. Two other cases had shock-like reactions, one after the eleventh injection of lycopodium extract, and the other after two years of grass pollen desensitization. While technical and dosage errors may account for reactions, in most instances of death from shock as well as of nonfatal constitutional reactions, no external causes, methodologic errors or overdosages have been demonstrable. Bruun[44] and Salén[296] both suggest that desensitization is a hospital procedure, and one would agree if the "rush" method is selected. Midttun[227] reported an anaphylactic death in an asthmatic patient occurring within ten minutes after the injection of 0.3 ml of a 1:10 dilution of an autogenous house dust extract. Burning of the tongue and cyanosis appeared very quickly, and it was assumed that an inadvertent intravenous injection had been given. Treatment had been started only eleven days before with a 1:100,000 dilution, and two to four injections were given a day. The advantages of such rapid hyposensitization appear dubious to the reviewer, because of possible cumulative effect. Therapy with bacterial vaccines likewise is not devoid of danger, according to Bruun.[44] In bacterial-allergic conditions, no more than five days should be permitted to elapse between vaccine injections in order to avoid the risk of bacterial-anaphylactic shock. If a marked systemic reaction occurs after an injection of bacterial vaccine, therapy should be interrupted for from three to six months.

TREATMENT: CLIMATOTHERAPY AND INSTITUTIONAL CARE

Change of climate as a mode of therapy in asthma presents many controversial aspects. In general, some patients are improved, but they are few compared with those either not improved or made worse, according to Marks.[211] Questionnaires to pediatricians and allergists in various parts of the United States revealed divided opinions regarding climatotherapy. Such benefit as may ensue was largely attributed to the lesser amounts of air-borne allergens in the new environment and to the interruption of recurring respiratory tract infections which interfered with specific therapy. The replies from specialists in Florida showed that most asthmatic children transported to Florida improved to a degree, some permanently, some temporarily. The long-range pattern of response could not be finally evaluated in less than two to three years. Many children, although

nonallergic in Northern climates, developed respiratory allergies in Florida. Marks concluded that the advantages of a uniformly warm climate should be considered only after all other therapeutic measures have been exhausted and after it has been determined if the anticipated area promises freedom from the existing offenders.

An Editorial[82] suggests that while climatotherapy, like other methods of therapy, falls far short of universal efficacy, its persistent popularity indicates that it must have a basis of fact. The reviewer wonders whether its "persistent popularity" is not more often a measure of desperation. In view of the tremendous economic adjustments involved in a permanent change of climate, there is a real need for facilities to care for asthma sufferers of limited means in the areas of favorable climatic conditions—preferably at first on a trial basis. It may be hoped that the release of facilities formerly devoted to tuberculosis may now be applied to the treatment of asthma. Such institutions will obviously require financial support on a national rather than a local level.

Hallowitz[144] reported that much of the benefits of residential treatment at the Jewish National Home for Asthmatic Children at Denver stemmed from the separation from the family and home environment, and from the casework therapy which helps the child overcome the insecurity, dependency, and inability to master the environment which characterize the personality problems of the asthmatic. During a period in the Home averaging two years, about half the children were entirely free of asthma, and an additional one-third had much reduced symptomatology. Full medical and allergic care was given, plus attention to the emotional factors by caseworkers, group workers, houseparents, psychiatrists, and the administrative staff. Casework with the parents was essential for lasting results. Huët[163] observed that about two-fifths of a series of asthmatic children remained free from attacks after entering an Asthma Center in the Netherlands, but these were the milder cases. The remainder continued to have attacks after admission.

TREATMENT: CORTICOTROPIN AND ADRENAL CORTICAL STEROIDS

The medical principles of adrenal steroid and corticotropic therapy, including a chapter on bronchial asthma by Rose, are considered in a book by Lukens.[206] A recent Medical Forum[222] outlined the opinions of M. S. Segal, T. G. Randolph, C. E. Arbesman, and A. S. Friedlaender regarding the indications for hormonal therapy of asthma. While differing attitudes were expressed, it is emphasized that such therapy is not a cure-all, that it does not replace any or all other forms of therapy, that it is often unsatisfactory as a long-term therapeutic approach, that difficulties and problems attend withdrawal, and that it is probably best reserved for cases of status asthmaticus and those not responding to long-established therapies.

Several reports were incorporated in last year's review[131] prior to their publication. For those readers who might wish to consult the complete articles, these references are appended: Irwin et al[168] regarding undesirable cortisone effects, particularly osteoporosis; Bickerman and Barach[28] comparing the results with corticotropin, cortisone and hydrocortisone; and Arbesman and Richard[10] and Baldwin et al[14] concerning prolonged therapy with these agents.

Cortisone.—A "blind" trial of oral cortisone was conducted in thirteen severe cases of asthma by Brockbank and Savidge,[36] fourteen others re-

ceiving an indistinguishable placebo. This is claimed to be the first such study. Three of the control subjects did so poorly clinically that they were subsequently given the drug. Of the treated group, six patients were markedly improved, and were able to resume their usual activities; four were improved, but mostly subjectively; one was no better and died eight months after the trial; two patients died while taking the drug. (These two fatalities were reported separately.[303]) In the placebo group, more than half failed to improve; one died. The longest remission after the withdrawal of the drug was eleven weeks, but most cases relapsed in a few days. In a later report by the same authors,[302] covering oral cortisone treatment of thirteen patients for periods of seven to eighty weeks, enthusiasm was somewhat tempered, although undoubted benefit was claimed. Much of the improvement was attributed to the euphoria and to the weight gain induced by the drug. It was recommended that when asthma cannot be controlled with less than 100 mg. of cortisone daily, the treatment should be abandoned.

Hortling and Wegelius[158,159] gave cortisone orally to ten patients for from four to twenty-six months. All improved considerably, seven becoming able to live normal lives. Although one patient already had osteoporosis and one had hypertension, no untoward effects were noted, except marked weight gain in one other subject, requiring temporary discontinuance of the drug. Turiaf et al[356] treated twenty-two patients with severe continuous asthma for periods of three to twenty-four months. The minimal maintenance dose was usually between 50 and 75 mg. per day taken five days each week. Testosterone was administered intramuscularly once a week. Results were excellent in all except one patient who developed cavitational pulmonary tuberculosis during the eighteenth month of treatment.

Herxheimer[156] showed that after four days of oral cortisone therapy, eleven chronic asthmatic patients in eighteen experiments were able to tolerate two or three times as much aerosol of their specific allergens (grass pollen or house dust) as before. Whereas this amount would previously have caused violent and severe paroxysms, under cortisone therapy attacks did not occur or, at most, a harmless and transient wheeze. When the exposure was repeated later with the subjects under reduced cortisone dosage, and again after the drug was stopped, tolerance was still found to be elevated. Cortisone greatly facilitated and shortened the course of bronchial hyposensitization by the inhalation route.

Hydrocortisone.—The effectiveness of oral hydrocortisone in perennial bronchial asthma was reaffirmed by Schwartz,[307] Fyles and Rose[115] and Turiaf, Marland and Jeanjean.[357] In a series of cases started on 80 mg. per day, rapidly reduced to the smallest amount maintaining symptomatic relief, Schwartz[307] obtained excellent relief in twenty, marked in five, moderate in nine, slight in one, and no response in four instances. In those who had previously taken cortisone, the hydrocortisone proved superior in one-third, and equally effective in most; none did better with cortisone, and one patient failed to respond to either drug. Side effects from hydrocortisone appeared in six cases (all of whom had had similar effects from cortisone), and required discontinuance of therapy in one because of sweating, tachycardia, and dizziness. Fyles and Rose[115] also found the results in fifteen patients comparable to those with cortisone, but requiring somewhat smaller dosage. Symptoms began to subside in less than

forty-eight hours in all but two cases, and virtually disappeared in one to six days in all but one case. The smallest effective maintenance dose was usually 20 to 40 mg a day, but one patient required 80 mg per day. Side effects were few in the two or three-month period of therapy, slight edema appearing in three cases, and headache and palpitation with transitory hypertension in one. Relapses occurred in from seven to ninety days after cessation of treatment. Turiaf et al[357] observed immediate satisfactory results in all but three of fifty-two patients given initial doses of 60 to 100 mg daily and subsequent maintenance dosage of 30 to 40 mg daily for five days each week. Testosterone was administered weekly by intramuscular injection. Hydrocortisone was found as effective as cortisone in approximately two-thirds the dosage.

Traynor and his co-workers[346] reported good or excellent results in each of seven cases of ragweed asthma given hydrocortisone for two to twenty-six days during the height of the season. Daily dosage ranged from 30 to 160 mg. All the patients had failed to respond to usual therapy. The asthma tended to recur when the drug was stopped. While the optimal dosage was not clearly determined, an initial dose of 80 mg per day seemed adequate for most. While hormonal therapy is not regarded as the treatment of choice for seasonal asthma, its use is justified in selected cases of pollinosis.

Corticotropin.—In a "blind" controlled study, Ball[15] found that five of six patients with severe chronic asthma given injections of corticotropin showed moderate to marked improvement, while only two of seven cases improved when given physiologic saline solution on the same schedule. The dosage of ACTH was 25 mg every six hours for seven days, followed by the same amount at longer intervals, to a total of 1 gram in twelve days. Two cases had not relapsed after two and thirteen months, while the others, relapsing in one to twenty-three days, responded to a second course. One patient died with cor pulmonale subsequently. Three patients showed marked fluid retention. Of seven other cases with status asthmaticus, three improved greatly, an equal number slowly, and one died within twenty-four hours. Twelve patients with severe asthma were maintained on corticotropin with satisfactory results, the symptoms usually becoming mild.

L. N. Gay and Murgatroyd[121] used a purified corticotropin in gelatin in a series of seventy-eight ambulatory patients. One injection of 60 to 100 units was given the first day, with diminishing dosage, depending on the response, for five to seven days. Generally excellent results were obtained, although a few responded poorly. However, in the older age groups, relapses occurred more frequently, as did side effects. Nevertheless, patients with hypertension, diabetes, coronary occlusion, chronic sinusitis and pronounced emphysema were treated under careful observation and did well. Seventeen patients are receiving maintenance therapy from once or twice daily to two or three times a week. Side effects of sufficient severity to require stopping the treatment occurred in only one instance. There were no local reactions in approximately 2,000 injections of the repository form of ACTH, and no evidence of the development of resistance to or sensitization to the hormone.

Fyles and Rose[114] employed a long-acting aqueous preparation of ACTH in a vehicle containing 1.5 per cent of carboxymethylcellulose (Duracton®). This preparation had few of the disadvantages of previous repository types, requiring no heating. It appeared to be somewhat more potent than

other repository forms of corticotropin and to be effective for a longer period of time. Thirty courses lasting from two to 239 days were given to twenty patients, with initial doses of 10 to 80 units and later maintenance doses usually in the range of 10 to 30 units every second day. All but three cases had complete or nearly complete relief. Symptoms began to subside in most instances within twenty-four hours, and nearly always within forty-eight hours. Side effects were few, but transitory urticaria appeared in two instances. In contradiction to the observations of others, it was noted that the drop in circulating eosinophils showed some parallelism to the clinical improvement.

According to Johnson,[173] only fourteen of 407 patients with asthma admitted to the hospital were refractory to the usual measures. These were given 25 mg of corticotropin by intravenous infusion at a rate of 20 to 30 drops per minute over a period of at least eight hours. On each of the next two or three days, 5 to 10 mg was administered in the same way. Thereafter, oral cortisone was given for five to seven days. Initially, half the patients were benefited within twelve hours, and the remainder, except for one patient who was not improved, within forty-eight hours. Two of the patients were given a second course of ACTH with decreased effectiveness and two with a satisfactory response. In addition to the immediate benefits, it appeared that patients tended to respond more readily to ordinary measures when subsequent relapses occurred. The clinical and endocrinologic studies of Cohen and Sulman[57] suggested that corticotropin may be administered in dosages much smaller than those commonly employed and still give full therapeutic benefit without undesirable side effects. A daily intravenous infusion of 5 mg or less in 500 to 1000 ml of 5 per cent glucose solution was given at a rate of 12 to 16 drops per minute. Thus, in two cases of asthma, the average daily dose was 2.1 and 1.5 mg for a total of 17 and 11 mg in eight and seven days, respectively. The largest dose on any one day was 3 mg. Four other cases given 10, 15 or 20 mg daily for six to twenty-five days did no better clinically and often developed moon facies or other side effects. It is suggested that the intravenous administration of small doses (1 to 5 mg per day) represents a physiologic approach to treatment giving optimal results and may be of particular value in patients with hypertension, heart disease, or diabetes.

Cortisone and Corticotropin.—Several reports deal with both hormones in the treatment of asthma. Unger and Unger[363] stated they should be used only where the patient's life is endangered (when prompt intravenous administration is indicated), or when improvement does not follow other adequate therapy and then after weighing the possible disadvantages and contraindications. Of fifty asthmatic patients, ten were given ACTH, thirteen cortisone, and twenty-seven both. The results were excellent in sixteen, good in twenty-six, and poor in eight cases. When the hormone was stopped, relapses occurred in sixteen instances. Half the cases are still under therapy. The hormones may be used to alleviate symptoms so that skin testing may be performed. They may cause allergic reactions ranging from urticaria to anaphylactic death. They do not cure, and even prolonged use does not change the underlying allergic state. Unger[362] reviewed the indications for steroid therapy elsewhere.

Brown[38] found that 5 to 10 per cent of a series of 300 cases were not helped; most received oral cortisone or ACTH gel by injection, while some were given cortisone hypodermically or aqueous corticotropin intra-

muscularly or intravenously. A few cases not relieved by oral cortisone were benefited by corticotropin by injection, and *vice versa*. The literature indicates that 85 to 95 per cent of asthma sufferers derive prompt benefit from steroid therapy. Vallery-Radot et al[365] felt that such therapy should be reserved for severe cases, particularly status asthmaticus. It is deemed to have only symptomatic and transitory effect, and while the benefit is often spectacular, it is almost always of short duration. Irwin and Burrage[167] found oral or injectable cortisone more useful in seasonal and nonseasonal, pediatric and adult asthma than corticotropin. Walther[371] stated that these drugs should not be routinely used in asthma in children, but are indicated in threatening situations of long-continued and stubborn attacks of the type of status asthmaticus. Buffum[45] decries their use in infants under one year of age.

Unusual Methods of Administration and Combinations with Other Therapy.—Several investigators, many of them abroad, have tried hormonal therapy by unique channels of administration or in conjunction with other treatment modalities not usually employed simultaneously.

Intracutaneous injections of corticotropin in a specially prepared vehicle of partially hydrolyzed gelatine solution were given by Sangiorgi.[301] Doses of 5 to 20 mg were divided among three or four injections a day. Later doses were given daily, and then at intervals of two or three days, for a total course of 75 to 200 mg. The local wheal and erythema faded in about twelve or twenty-four hours, usually leaving a small indolent nodule which disappeared in two or three days. Half of a series of six cases had a prompt cessation of the crisis, the others improving less rapidly. The advantages claimed for this method are low dosage, economy, safety, and fewer side effects. Seyberlich[317] also claimed impressive results in thirteen cases of asthma including four who also had gout, from intradermal injections of 10 units of ACTH, along with 0.125 mg of a histamine salt and 0.04 gram of a histidine salt. Treatment was repeated as necessary. Prompt symptomatic response was noted.

The intranasal application of a specially prepared, highly purified corticotropin in proper particle size was shown by McKendry et al[218] to be physiologically and clinically effective. Its influence on circulating eosinophils and 17-ketosteroid excretion was comparable to that given intramuscularly. (It may be noted that ACTH administered orally or by aerosol is inactive.) Most of the subjects were initially given 20 to 40 units of corticotropin in each intranasal administration twice a day. Varying dosage schedules were subsequently employed, but the usual effective daily dose was 60 to 80 units and the smallest maintenance dose was 10 units a day. Three of four patients responded well, often showing clinical benefit in a few hours. The only untoward reactions were some nasal irritation and occasional sneezing for a few minutes after the application. The unsuccessful case also failed to respond to intramuscular corticotropin. It is suggested that the intranasal approach may be a practical method for administering ACTH to ambulatory patients.

Although investigating rhinitis primarily, Rohen[288] found that the intranasal instillation of a hydrocortisone suspension (20 mg per cc) reduced the frequency and severity of asthma attacks accompanying allergic rhinitis. It was not deemed advantageous to add an antibiotic or an antihistaminic to the material.

Diament and Kallós[71] and Robecchi and Cartesegna[282] claimed favorable

results from intrabronchial steroids. The latter investigators employed an aerosol of diluted hydrocortisone acetate. Although only one to four treatments were given, six of seven cases showed improvement lasting for hours, days, and even up to two months. Diament and Kallós[71] instilled 25 mg of cortisone in each main bronchus by way of either the bronchoscope or a laryngeal catheter ("Larynxspritze"). Tetracaine was sometimes added to the suspension. Five or six instillations in twenty weeks were well tolerated, and improvement after a single treatment persisted for some days or weeks. Turiaf[351] recommended buccal administration of cortisone in small doses for asthma with continuous dyspnea.

Finke[94] advocated combined therapy with cortisone and antibiotics in asthma associated with respiratory infection, not only as a palliative, but even more to prevent paroxysms and complications. In "intrinsic" asthma, pyogenic obstructive bronchitis is nearly always present. Brief antibiotic therapy fails to eradicate suppurative bronchopulmonary infections. Antibiotic therapy with penicillin by various routes of administration and/or streptomycin or broad-spectrum antibiotics for an average of nearly three years, combined with cortisone therapy for an average of three and one-half months gave excellent or good results in 80 per cent of seventy-eight patients with asthma. In early cases, and especially in children, the improvement often approached a "cure." The combined therapy seemed to speed the improvement, led to longer remissions, and permitted the use of cortisone in smaller dosage. Fear of possible dangers should not be a deterrent to the proper use of these agents. Side effects were noted in six instances from the antibiotics and in eleven from the cortisone. Arbesman[9] in commenting on this method, pointed out the difficulty of establishing the diagnosis of infectious asthma and of identifying the causative organism, as well as the risks of antibiotic prophylaxis and of long-continued cortisone therapy. Extrinsic allergy, if present, should also be treated.

Sánchez[299] reported that the simultaneous administration of 300 cc of whole blood from a donor of the opposite sex while 25 units of ACTH (with ascorbic acid added later) were given intravenously in the opposite arm was effective. Six patients with asthma given two such treatments at a three-day interval remained asymptomatic for eighteen months, while one was much improved after three infusions.

Kühne, Schmidt and Kania[190] combined cortisone treatment with fever therapy. The latter was achieved by a sterile turpentine abscess in one group of patients, and by injections of milk or of nonpathogenic pyrogenic bacteria (Pyrifer) in another. One group was given only cortisone. The drug was given for five days in dosages of 25 or 50 mg four times daily. The results were generally favorable, with only three therapeutic failures in forty cases of status asthmaticus and severe prolonged asthma, but were particularly gratifying with the turpentine-abscess group. Remissions lasted for six weeks to six months, but the relief was only temporary.

Nitrogen mustard was given immediately after intravenous corticotropin by Herraiz Ballestero[153] to four patients who had previously been given each drug alone. A typical schedule was 20 units of ACTH and 3 or 6 mg of nitrogen mustard. It was noted that the combined treatment greatly reduced the nausea and vomiting following injections of nitrogen mustard and gave better clinical and pulmonary function testing results, and far more prolonged remissions (up to forty-five and sixty days) than did either drug alone.

Groen's[138] use of psychotherapy in conjunction with corticotropin treat-

ment and Comeau's[60] simultaneous hyposensitization have been mentioned earlier.

It is noteworthy that all these advocates of "combined" therapy claim that smaller doses of the hormones are effective because of the ancillary treatment, and nevertheless yield better results. Further evaluation of these and other methods of enhancing the efficacy of steroid therapy seems indicated.

Side Effects and Dangers of Hormonal Therapy.—It is not the reviewer's intention to repeat here the various endocrinologic and electrolytic effects of this form of treatment, since they have been amply covered in older literature. Attention will be called to recent reports and unusual reactions, especially in asthma patients.

Segaloff[316] looks upon cortisone, and incidentally ACTH, as a "triple-edged sword." In addition to their salutary effects and the usual immediate untoward results, there are a series of delayed deleterious effects which, if not recognized, may actually result fatally. These delayed effects may not be apparent for months or even years after the discontinuance of the drug. They result from insufficient adrenal cortical reserve to meet stress, such as trauma, illness or surgery. It may be assumed that patients receiving sufficient cortical hormone therapy to produce signs and symptoms of hypercorticism have atrophic adrenals for at least one year after cessation of therapy. It would be wise for patients given steroids or ACTH to carry a card indicating the dosage, and this should be continued for one year afterwards.

An Editorial[81] points out the responsibility of the physician to be familiar with and alert in detecting undesirable side effects. He should remember, among others, the possibility of decalcification of the skeleton to the point of collapse of vertebral bodies and pathologic fractures, during prolonged administration of cortisone. When a surgical operation proves necessary in a cortisone-treated patient, there is need for special pre- and post-operative cortisone therapy. The balance of the evidence indicates that, when a severe acute infection arises, it is unwise to stop the drug abruptly and safer to continue it while using appropriate antibiotics. In chronic asthma, a reasonable degree of relief by a relatively small dose which may require other symptomatic measures at times is probably preferable to an attempt to control the symptoms completely by cortisone alone. Prolonged steroid therapy should not be undertaken lightly.

In about 400 cases treated with adrenocortical compounds, Rose[289] found two spontaneous fractures of vertebrae, three cases of psychosis, diabetes-like changes in ten patients, of whom two required insulin, and no instances of tuberculous spread or activation of peptic ulcer. Five patients underwent major surgery while on cortisone without untoward reactions. In a number of cases on continuous therapy for three or four years, no evidence of permanent adrenal suppression was observed.

Brown[38] pointed out that, in an allergic population receiving ACTH, approximately 2 per cent may be expected to evidence urticaria, angioneurotic edema, anaphylactic reactions and shock, or bronchial asthma. Cortisone has been known to cause asthmatic reactions. Swift[334] reported an anaphylactoid reaction occurring one hour after the thirteenth injection of corticotropin in a thirty-five-year-old asthmatic woman. Intradermal skin tests were positive to aqueous porcine ACTH (less so to the highly purified gel preparation), to aqueous beef ACTH, and to anterior pituitary

extract, but were negative to pork, beef, posterior pituitary extract, and pitocin. Passive transfer tests gave similar results.

Two deaths occurring during cortisone treatment of asthma were observed by Savidge and Brockbank.[302,303] The literature revealed at least eight asthmatic patients dying while on either cortisone or corticotropin therapy. It is felt that the drugs may be dangerous to life under some undefined conditions and that anaphylaxis may possibly play a part. The death in status asthmaticus of a fifteen-year-old boy given steroid therapy for Besnier's prurigo (disseminated neurodermatitis or atopic dermatitis) occurred one week after treatment was stopped, according to a British report.[101] Death from anaphylaxis occurred in New Zealand following an injection of bovine corticotropin for exudative dermatitis.[98] Porcine corticotropin had previously been tolerated, but an injection of bovine material nine months before the fatality had caused a severe shock-like reaction.

According to Sandweiss[300] and Wollaeger,[378] acute peptic ulcers may occur during cortisone or corticotropin therapy, whether or not the patient has previously had an ulcer, and may lead to perforation, hemorrhage, and even death. There seems to be no correlation with the dosage or duration of therapy. Other possible gastrointestinal complications of steroid treatment include ruptured gallbladder, ruptured Meckel's diverticulum, intestinal or colonic ulcerations and perforations, ulcerative esophagitis, and phlegmonous gastritis.

Newer Preparations.—A change in the chemical structure of cortisone and hydrocortisone introducing a double bond between C_1 and C_2, accounts for prednisone (Metacortandracin® or Meticorten®) and prednisolone (Metacortandralone® or Meticortelone®) respectively. Although no published reports on their use in asthma have appeared at the time of this writing, preliminary information[35] indicates that they are effective in one-third to one-fifth the dosage of the older steroids, less likely to affect electrolyte balance, and much less prone to cause side effects.

Wakai and Prickman[368] found that a synthetic halogenated steroid, 9α-fluorohydrocortisone acetate, had only a variable effect on asthma and that edema and weight gain occurred in most cases.

TREATMENT: SURGERY

In a follow-up study, Johnston and Watkins[174] evaluated the effect of tonsillectomy and adenoidectomy in thirty-one asthmatic children. The series was small because of generally poor results in the past. According to the parents' replies to a questionnaire, the asthma showed improvement in about two-thirds of the cases, and was more likely to do so in the older age groups, over four years of age. The findings were at variance with those in another group of twenty-two children receiving a longer follow-up: seven gave a history of the development of asthma for the first time shortly after tonsillectomy; an equal number had had asthma previously and were not benefited; five were made worse. Only three manifested improvement, and this was only temporary, never for more than nine months. An occasional brilliant result was seen in those older children whose nutritional state was impaired and in whom it was clear that tonsillar infection always preceded the asthmatic paroxysms. Bowen[33] and Walther[371] counsel extreme conservatism in performing tonsillectomy and

adenoidectomy in asthma patients, and reiterate that lymphoid hyperplasia and lymphoid nodule recurrences in the vicinity of the pharynx are usually secondary to the allergic state.

Szokodi-Dimitrov[340] reviewed the surgical approaches to the therapy of asthma and concluded that interruption of both the sympathetic and parasympathetic fibres to the lungs is necessary. He devised such an operation, transecting the pulmonary branches of the vagus and the sympathetic trunk below the fifth thoracic ganglia, along with ganglionectomy. The procedure, first on the right side and then on the left side one to three months later, was carried out in ten cases; four additional patients have had only the unilateral operation as yet. Since the longest period of observation has been twelve months, only preliminary evaluation was possible, but the results were stated to be very encouraging. Even after the unilateral procedure, the asthmatic attacks became less frequent and severe.

Fitz-Hugh[96] considered the management of sinusitis in asthmatics, 75 to 80 per cent of whom are said to show gross changes in the paranasal sinuses. The indications for sinus surgery in asthma are given as: (1) pathologic changes in the sinuses requiring surgical attention on their own merits; (2) minor or moderate sinusitis in conjunction with persistent asthma not responding to prolonged conservative therapy; and (3) cases in which minor nasal procedures, such as sinus lavage or polypectomy, often prove of definite benefit. After minor rhinologic surgical procedures in bronchial asthma, improvement was noted in 75 per cent, along with a few cures. After major or more extensive surgery, about half improved, while about half did not, and of these about 18 or 20 per cent noted aggravation of the asthma. Aside from this, about two-thirds had improvement in the nasal and sinus condition, about 30 per cent had indifferent results, and in 5 per cent the condition was aggravated. Taub and Rosenberg[343] presented a plea for conservative and medical management of nasal polyps. They noted that after surgical removal, some patients experienced an immediate exacerbation with an increase in the severity of the cough, sneezing, nasal obstruction, dyspnea, and wheezing. Some patients went into status asthmaticus. The results were stated to be even worse when radium therapy was given two weeks after the surgical extirpation of the polyps.

The surgical risk of the elderly asthmatic patient was discussed by Fromer.[109] With proper allergic pre- and post-operative control, such cases are a relatively safe operative risk. Proper management encompasses attention to feather pillows, flowers, diet, and smoking. Iodides and bronchodilators are administered. If rapid control of the asthma is required, intravenous corticotropin is preferred, although cortisone may be used. An "antibiotic umbrella" is added. Antibiotics are given, even if steroids are not used, if there are indications of pulmonary infection. Penicillin and streptomycin are the most generally useful. Gas-oxygen-ether anesthesia is favored, although spinal anesthesia is safe. All agents of histaminic, cholinergic, or vagal action, including curare, are contraindicated. Extreme gentleness in manipulating the endotracheal tube is enjoined, since even under the best circumstances, laryngeal edema or spasm may ensue. At the end of the operation, special care is taken to ventilate the lungs. Postoperative oxygen is rarely needed, but may be given with helium or the intermitttent positive pressure technique.

Adriani[2] covered the subject of anesthesia and allergy, including a

number of observations pertinent to asthma. Allergy to inhalant anesthetics is uncommon and to nonvolatile drugs used for general anesthesia or as adjuncts to anesthesia is rare. Bronchospasm is not necessarily obviated in an anesthetized subject. Since ether, vinyl ether, chloroform, and trichlorethylene are bronchodilators, they may be used in asthmatic patients. Atropine or another anticholinergic drug is necessary as preanesthetic medication to inhibit the secretion of mucus. Bronchospasm may occur during induction, but disappears when anesthesia is fully established. Theoretically, cyclopropane should be avoided because of its bronchoconstrictor effect, but most persons with asthma tolerate it without difficulty and, unlike nitrous oxide and ethylene, it permits adequate oxygenation at all times. The thiobarbiturates are spasmogenic and may precipitate persistent bronchospasm. Narcotics, both opium alkaloids and synthetic analgesics such as Methadon, Nisentil® and Dromoran,® depress respiration and may cause bronchospasm or enhance it, if it exists. Meperidine (Demerol®) is not spasmogenic but causes respiratory depression in large doses. It is preferred to the others when a narcotic is indicated. Curare, tubocurarine and its derivatives, and the parasympathomimetic drugs, eserine, neostigmine and edrophonium, are all capable of initiating intense bronchospasm. Muscle relaxants and their antagonists are best avoided in persons with asthma. Vasopressors and sympathomimetics, such as epinephrine, norepinephrine, and desoxyephedrine, are not objectionable but should not be given simultaneously with cyclopropane and trichlorethylene since they may cause cardiac irritability and precipitate serious arrhythmias. Cortisone and related hormones should not, if the patient is receiving them, be discontinued at the time of operation.

Brush[43] noted that when patients with asthma require surgery, their course during anesthesia and postoperatively is greatly improved by the administration of hydrocortisone. Other advantages include modification of transfusion reactions and the control of serum sickness and drug sensitivities.

TREATMENT: VACCINES AND ANTIBIOTICS

On the basis of thirty years' experience with 364 cases of pediatric asthma and more than 1,500 bronchoscopic examinations, Crump[63] advocates autogenous vaccine therapy, but greatly favors bronchoscopic vaccines. Culture frequently yields a single organism, most often nonhemolytic streptococcus or *Streptococcus viridans*, and this often differs from that obtained on nose or throat cultures. Mixed flora, when present, may also include nonhemolytic *Staphylococcus albus*, hemolytic streptococcus, nonhemolytic *Staphyloccus aureus* and others. When the child has received an antibiotic, less pus is present, but enough is still available for culture and vaccine. The vaccine is given subcutaneously each week in small dosage until the patient has been asymptomatic for at least a year, and then at longer intervals. Vaccines prepared from sinus washings, tonsils, or nose and throat secretions have also been used, especially when bronchoscopy is refused, as well as bacterial filtrates and stock vaccines. However, the results from all these have not been as favorable. Stuppy[331] prefers the intradermal route for vaccines, and notes that the results are not reproducible and that vaccine therapy may aggravate nonallergic asthma. On the other hand, Bowen[33] is very critical of vaccine therapy, having observed no difference between groups of children given autogenous vaccines, stock vaccines, or a placebo.

Longacre[203] discussed the principles of antibacterial therapy in infectious asthma. The problem is to analyze the possibly significant factors in those cases failing to respond. The bacterial findings usually indicate a mixed flora and while only one of the recovered species may theoretically be the etiologic pathogen, there is no way of proving this. It is of little clinical importance whether the possible allergen is an exotoxin, endotoxin, bacterial protein, split protein resulting from enzymatic or fermenting action, or any other part of the infection. The site of the infection associated with infectious asthma may be in the upper respiratory passages or in the deeper bronchi and terminal bronchioles. It is debatable whether infections with similar features elsewhere in the body are capable of causing asthmatic seizures. Infectious asthma probably exists in two forms: the perennial and more common, in which the infection precipitates the attack, and the type in which asthma exists only at the time of an acute infection. The perennial type seems less responsive to antibacterial therapy. Studies concerned with establishing criteria for the diagnosis of infectious asthma should prove of value. The rational selection of an antimicrobial agent is essentially a laboratory problem. Antibiotic sensitivity tests show that individual strains of a single species may show extremely wide variations in sensitivity levels. Successive episodes in the same patient may not be the same bacteriologically or in antibiotic responsiveness. Since infectious asthma is a chronic recurrent disease, supportive therapy to increase resistance to infection and, in selected cases, possible immunologic therapy are essential. Failure of antibacterial therapy may be attributed to : (1) an incorrect evaluation of the significance of the infection as the cause of the asthmatic attack; (2) failure to administer an antibiotic effective against the particular infection; and (3) failure of the antibiotic to reach the site of infection.

Shuey and Grater[320] employed various combinations of procaine-penicillin, streptomycin or dihydrostreptomycin, Gantrisin®, and Bicillin® for periods of three to eighteen months. Generally good results were obtained. Of the antibiotics, all were considered effective, and none could be singled out as superior, except perhaps in the convenience of administration. Fein[91] found that treatment with the hydriodide of diethylaminoethyl ester of penicillin G (Neo-penil®) given intramuscularly daily for three days at the first evidences of respiratory infection gave better results than did potassium penicillin G in equal amounts, and even more so when compared to a control group given no antibiotics. However, the percentage of patients requiring hospitalization was approximately equal for each of the three groups. Neo-penil was well tolerated, except for a frequent complaint of pain at the injection site.

Blatt[32] reported that the administration of oxytetracycline (Terramycin®) concomitantly with desensitizing injections of bacterial filtrates, in cases of bacterial allergy, reduced the period of desensitization and resulted in clinical improvement more rapidly than injections alone. The length of treatment required was one-fourth as long, and clinical benefit appeared in one-third the time.

Allergic, anaphylactic, and even fatal reactions to penicillin have been accorded considerable attention. According to an extensive statistical compilation by Kutscher, Lane and Segall,[192] comprising 10,420 cases, systemic penicillin can actually cause asthma in 0.01 to 0.02 per cent of patients. Apparently other antibiotics and the sulfonamides do not do so, according to their information, although Mechetti[221] has recently reported

two instances of bronchial asthma occurring during streptomycin therapy of pulmonary tuberculosis. Strauch, Byrd and Eng[330] point out that the over-all incidence of penicillin reactions of all types has been variously estimated at from 2 to 20 per cent, and is highest in allergic patients. They reported two anaphylactic fatalities. According to Kern and Wimberley,[182] of the seventeen fatal cases of anaphylactic shock reported, five were in asthmatic patients. Rosenthal[293] described eight such instances, one in an asthmatic, and the necropsy findings in six. He suggested that asthmatic symptoms should be considered a contraindication to the use of asthma. Nemser,[245] although he observed three severe non-fatal reactions, disagreed in view of the benefits which penicillin may give, and it has been pointed out[55] that penicillin is actually the antibiotic of choice in asthma, the possibility of sensitivity being accepted as a calculated risk, except when a positive history is obtained. Contrary to most opinions, Nemser[245] holds that even the history may not be helpful. It has been granted[266] that intradermal skin tests are not infallible, but patients who are extremely sensitive to penicillin are the most likely to give a positive whealing response.

Kärcher[176] reminds us that penicillin may sensitize not only by injection, but also orally, topically, in lozenges, or by aerosol. A case in point was reported by Carter and Cope,[50] the patient suffering a severe anaphylactoid reaction shortly after applying some penicillin ophthalmic ointment to one eye.

There appears to be general agreement that no one type of penicillin is especially incriminated, that the procaine radical in certain forms is very rarely implicated, and that a history of previous reaction, however mild, constitutes a contraindication to further penicillin. Where doubt exists, another antibiotic should be chosen.

TREATMENT: AEROSOLS

Interest continues in the aerosol method of administering antimicrobial, mucolytic, wetting, bronchodilating, detergent, and other agents, as well as water-mist and alcohol in the treatment of asthma, asthmatic bronchitis, and some of the complications of asthma. Some of the individual agents encompass more than one of the properties mentioned. Adequate comparisons are impossible because of the frequent employment of more than one substance in a single aerosol and the use of various types of apparatus and treatment schedules. It is perhaps conservative to state that, aside from the bronchodilating and some antibiotic drugs, aerosol therapy with the other agents may be considered to be still in the investigative stage. Kopf[187] devised a modification of the instruments, employing a reservoir which maintains a constant fluid level in the nebulizer, requiring a minimum of supervision and preventing waste.

Imperato[166] reported good results from bronchodilating drugs such as isopropylarterenol and procaine in fifty-two children with asthma or asthmatic bronchitis, given usually four times daily. Penicillin and streptomycin were sometimes also incorporated in the aerosols. Side effects were rare. Karp et al[179] tried disposable plastic inhalers (dispolators) each containing 50 mg of dihydrostreptomycin sulfate "dust." The material was inhaled from six inhalers daily for three to ten days, depending on the chronicity of the symptoms. While favorable results were seen in bronchiectasis and chronic bronchitis, cases of bronchial asthma usually failed to respond, although occasional improvement occurred when there

was bacterial invasion. Results were not spectacular in allergic bronchitis, although secondary infections seemed to be prevented. Allergic reactions to the treatment occurred in 1.7 per cent of cases, this being less than with penicillin "dust." It was noted in the answer to a Query[265] that 5 per cent ammonium chloride is a very useful aerosol in bronchial disease due to obstruction predominantly by mucus and is much less likely to induce hemorrhage than such débridement agents as trypsin.

Alevaire® is a mucolytic aerosol detergent containing 0.125 per cent of superinone, 2 per cent sodium bicarbonate, and 5 per cent glycerine. The benefits of the removal of viscid mucopurulent secretions in asthma and other conditions is obvious, especially since bronchospasm and wheezing may be secondary to the presence of irritating bronchial secretions. J. B. Miller and his colleagues[229] employed Alevaire either by a tent method for overnight therapy or by a nebulizer with direct application of a nasal tip to the external nares for periods of thirty to sixty minutes. The latter method was used in the less severe cases and was preferred by the patients. It was suggested that various techniques employing hoods, masks, oxygen tents, and modified Croupettes might be employed. In eleven asthmatic adults, many presenting status asthmaticus, pulmonary fibrosis, emphysema, sinusitis, and other complications, the degree of benefit correlated closely with the presence of thick copious secretions or semi-solid mucous plugs. With the easier expectoration in one or two days and the elimination of secretions in one or two weeks, there was a corresponding decrease in the other symptoms of cough, wheezing, and dyspnea. Asthma with pure bronchospasm and without secretions sometimes responded, but not as uniformly. It was noted elsewhere[270] that Alevaire mist may produce severe irritation of the bronchial tree. The danger of detergent mists lies in the liquefaction of large quantities of secretions, so that the patient may drown in his own secretions unless the excess fluid is aspirated from the bronchial tree. Reactions to mixtures of antibiotics and wetting agents may be due to the former. Asthma, anaphylactoid reactions, and various skin eruptions have been reported. Hansen-Pruss and Charlton[150] found the following aerosol useful in elderly patients with emphysema when given every four to six hours: isopropylarterenol (1:200) 1 part; 50,000 units of crystalline procaine-penicillin 1 part; and Alevaire 2 to 3 parts. Other antibiotics may be used.

Sterling[328] deplored the improper use and abuse of epinephrine and isopropylarterenol aerosols, as well as isopropylarterenol sublingually. The ease of their self-administration readily leads to excessive use by patients. Cardiac, vascular or pulmonary side effects may be caused. Continued use of adrenergic agents, in addition to producing tachycardia, may weaken the myocardium and cause a mild form of bronchopulmonary congestion, inducing further dyspnea and asthma; thereby, a vicious cycle is set up. A useful list[278] of the constituents of the commercial bronchodilator inhalant solutions in Great Britain has been published. A similar list for the American preparations—and for the numerous other asthmatic medications and mixtures, for that matter—would be widely appreciated.

Segal et al[315] reviewed the advances in inhalational therapy, including their experiences with pancreatic dornase (desoxyribonuclease of pancreatic origin), usually administered along with Vaponefrin.® Treatment with 50,000 to 100,000 units every six to eight hours for two to six days gave maximum benefit in tracheobronchial evacuation. It was sometimes given by means of the intermittent positive pressure apparatus.[312,315]

Uhde[360] claimed good results in seventy-two patients given aerosol therapy twenty to thirty times in a period of two or three months, each treatment consisting of 2 cc of a solution containing 0.12 gram of Euphyllin (theophylline ethylenediamine). The results were better and the relief more prolonged than with oral or parenteral administration of the same drug. Antibiotics may be added to the solution.

Habeeb and his co-workers[142] considered trypsin aerosol a useful adjunct in the treatment of asthma. Twenty-seven of thirty-one patients given 125,000 units daily for four to seven days had good results as judged by increased vital capacity and decreased cough. The cases were selected on the basis of a thick tenacious sputum. The duration of benefit varied markedly, sometimes lasting only a few hours. Biron and Choay[29] reported gratifying results in a variety of nontuberculous bronchial obstructions, specifically in eight of eleven cases of infectious bronchitis in patients with asthma, and in fifteen of twenty-one cases of paroxysmal bronchial asthma. The dose was 125 mg of trypsin in aerosol form with a small amount of added isopropylarterenol (Aleudrine) twice a day. This was repeated for two days, rarely longer. Liquefaction of the bronchial secretions apparently began within a few minutes. Bronchoscopic aspiration was frequently avoided by this method and, when needed, was more easily performed. Occasional allergic reactions occurred, but were readily controlled. However, A. H. Unger[361] found the results of aerosol trypsin very disappointing in asthma. Only five of thirty-three cases with chronic asthma and emphysema gave good results; eighteen were therapeutic failures. In a smaller group with paroxysmal asthma, the results were better, but valid conclusions could not be reached. The therapy was especially helpful when the asthma was accompanied or complicated by infectious bronchitis or pneumonitis.

Kwasniewski[193] pointed out that the burning of the solanaceous alkaloids, hyoscyamine and atropine, contained in belladonna, hyoscyamus and stramonium leaves, has long been used in various preparations, although little is known of their pharmacologic effects by this method. He demonstrated that only about 30 per cent of the alkaloidal content passed over with the fumes and estimated that much less would reach the bronchi in actual use; with "asthma cigarettes," the greatest part remained in the butts. No pyridine compounds or pyridine base could be identified in smoke from burning nitrates or "saltpeter papers." Since all these preparations give inexact alkaloidal action, most of it being lost in the burnings or into the air, these methods are of little value. Kwasniewski recommended instead an aerosol of 5 drops of a mixture of 0.02 gram of atropine sulfate and 5 ml of a 1:1,000 dilution of epinephrine hydrochloride in 10 ml of glycerine, and diluted with water just before use.

Salomon et al[298] found that an aerosol of 0.33 mg of a new anticholinergic agent, Pamine® (epoxytropine tropate methylbromide) gave good protection against the bronchospastic effects of intravenous methacholine. Administration to seventy-nine patients with chronic asthma, either by direct aerosol or by intermittent positive pressure breathing, produced significant improvement in various pulmonary function tests, and the greater the degree of bronchospasm the more marked were the changes. While subsequent aerosols of isopropylarterenol or of racemic epinephrine caused even more marked improvment in the objective tests, some patients preferred the Pamine because of the absence of side effects. Better results were obtained with continuous nebulization than with the hand bulb. The

only side effects of Pamine were slight dryness of the oropharynx. There were no palpitation, tachycardia, blood pressure changes, headache, mydriasis or nausea. The possible advantages of combining the drug with an adrenergic agent are being explored.

Another anticholinergic drug, Antrenyl® (diethyl [2-hydroxyethyl] methylammonium bromide α-phenyl-cyclohexane glycolate) also produced consistent improvement in the pulmonary function tests when 0.5 mg was administered by aerosol to forty-five cases of asthma, according to Leslie, Dantes and Rosove.[199] Concomitantly, considerable clinical benefit was noted, marked or complete relief of the symptoms occurring in thirty instances. Control administration of water by the same intermittent positive pressure technique caused no significant objective or subjective improvement.

TREATMENT: PYROGENIC AGENTS

Subcutaneous, intramuscular, or intravenous administration of Piromen® (a sterile colloidal dispersion of polysaccharides derived from *Pseudomonas aeruginosa*) gave considerable improvement in about half of a series of asthmatic patients, according to Knight.[186] Exacerbations sometimes followed intravenous injection, so the other routes were preferred. Benefit, if any, always appeared before the sixth injection. The simultaneous employment of Pyrifer and cortisone by Kühne et al[190] has been mentioned above.

TREATMENT: RESPIRATORY EXERCISES AND MECHANICAL RESPIRATION

Favorable opinions regarding breathing and postural exercises and diaphragmatic training in the management of asthma and/or emphysema were expressed by W. F. Miller,[231] Dorinson,[72] Segal et al,[313] Barach,[19] and Schutz.[306] Dorinson[72] described the techniques of the commonly used breathing exercises. The aims are to deflate the lungs by increasing the expiratory phase, re-educate automatic diaphragmatic movement and diminish the thoracic component, mobilize the ribs and chest wall, and prevent kyphosis and other postural deformities. By familiarizing the patient with the mechanics of his desease, the exercises serve to lessen his fear of it. Barach[19] recommended training in the head-down and forward-bending positions, favoring increased diaphragmatic motion and so diminishing exertional dyspnea. Miller[231] found that the improvement following six to eight weeks of training in diaphragmatic breathing was reflected in improved pulmonary function tests; these included a striking increase in tidal volume at a lower respiratory rate and respiratory midposition, increased total ventilatory capacity, increased arterial oxygen saturation, decreased arterial carbon dioxide. and increased exercise tolerance with less dyspnea. Schutz[306] employed a modification of the Hofbauer technique of breathing therapy, including the prolonged "humming" expiration. This method along with various respiratory and graded muscular exercises was applied to twenty-three adults with bronchial asthma for from three to fourteen weeks. Good results were obtained in ten patients and improvement in nine others. Improvement was manifested by cessation or marked decrease in the number and severity of asthmatic paroxysms, an increase in the excursion of the diaphragm as demonstrated fluoroscopically or roentgenographically, and an increase of the vital capacity. The trained patients were often able to ward off an incipient asthmatic attack by means of the humming expiration. Ormis-

ton[251] noted that breathing and postural exercises often relieved the violent coughing associated with wheezing bronchitis or asthma in young children.

A contradictory note is sounded by Becklake et al.[22] Fifteen cases with varying degrees of chronic emphysema were submitted to breathing exercises or to breathing exercises augmented by faradic stimulation of the chest and abdominal muscles for periods of thirteen to sixty-two days. Observations were continued for twenty-three to 205 days, and each subject given three to ten complete batteries of pulmonary function tests. Though all but two patients claimed to feel better, the objective studies suggested probable improvement in only two, possible improvement in two more, and deterioration in three. In the remainder, no definite trends appeared. While there is a chance possibility that some other aspect of lung function not tested might have been helped, it seems more likely that the subjective improvement noted by the patients was the result of changed mental attitudes.

Elwell[85] employed continuous postural drainage for long periods (up to eighteen years) in several hundred cases of various respiratory disorders. The foot of the bed is elevated 18 inches or about 14.5 degrees and sometimes more. It is claimed that bronchial asthma, even when not obviously infectious, can be eliminated if treatment is started in the early stages; even in long-term sufferers very satisfactory results can be achieved, with some prospect of ultimately obtaining a completely asymptomatic state. Only three failures are admitted among thirty-one instances of continuous asthma.

Various forms of mechanical respiration have been under study. Trimble and Kieran[348] employed intermittent positive pressure breathing on inspiration (IPPB/I) with the Bennett valve using 100 per cent oxygen by means of a mask, on thirty-five patients with emphysema, including ten with primary bronchial asthma. Specific symptoms were improved in six or seven cases of the latter group. Benefit was often first noted within three weeks, but usually required four to six months for maximum improvement. It was impossible to predict which patients would be helped on the basis of the history, presence of infection, duration of disease, fluoroscopic examination, or physical signs. However, high-pitched sibilant expiratory râles usually indicated a favorable response while their absence had no prognostic value. It was emphasized that the therapy had to be continued for a sufficient length of time.

Segal et al[312] administered IPPB/I to ninety-five patients with asthma, employing either air or oxygen, and with or without a bronchodilator, for twenty minutes at a time, one to three times daily for five to sixty days. The clinical results were good or excellent in most instances. Benefits were not as marked in patients with chronic emphysema. IPPB/I with bronchodilator aerosols gave better results than either therapy alone. The vital capacity, timed vital capacity and maximum breathing capacity immediately after IPPB/I were usually lower than before, despite good clinical results. This was attributed either to pulmonary congestion or temporary fatigue. When bronchodilator aerosols were used simultaneously, these indices of ventilatory function were improved.

Exsufflation with negative pressure (E.W.N.P.) employing various cycling devices was tried by Segal et al[313,314] and Barach and Beck.[19,20] Barach[20] considers E.W.N.P. the most effective of the various physical methods for eliminating bronchial secretions. Nearly all of twenty-four cases of asthma were improved after such treatment. The immediate

effect when administered in conjunction with bronchodilator aerosols included an increase in vital capacity averaging 15 per cent, but only 9 per cent for the bronchodilator alone. The figures in cases of pulmonary emphysema were 42 and 36 per cent, respectively. It appeared that E.W.N.P. improved the effect of the bronchodilators. Repeated courses of E.W.N.P. therapy caused a 25 per cent increase in the vital capacity in cases of asthma. In those patients in whom bronchospasm was more prominent than retention of secretions, E.W.N.P. had little or no effect. The mechanically induced cough may be looked upon as a method of bronchial drainage.

TREATMENT: BRONCHOSCOPIC AND TRACHEAL ASPIRATION

Attention has been called to the value of bronchoscopic aspiration in selected cases of asthma by Anderson and Rubin,[5] Davison,[66,67] Léger,[197] Crump,[63] Stuppy,[331] Thomas,[344] Minor,[232] and Bernstein and Klotz.[26] The first-named, in discussing the otolaryngologic procedures useful in treating allergic patients, stated that it is unfortunate that bronchoscopy is still virtually neglected in asthma, and go so far as to recommend that the allergist should receive training in bronchoscopy. One might wonder if the allergist would employ the technique sufficiently often to maintain his proficiency. Aside from its value in differential diagnosis and in detecting a complicating bronchiectasis, bronchoscopy is of obvious benefit in status asthmaticus and sometimes effects its termination. Davison[66,67] bronchoscoped thirty of fifty patients with infectious asthma, sometimes as often as six to ten times in a single case, to remove the gummy endobronchial exudate. Results were generally favorable, although bronchospasm may be temporarily increased, and the mucosal edema and submucosal infiltration obviously not relieved. It seems that the patients who have persistent asthma for two weeks or more are the most likely to benefit from bronchoscopic aspiration. Preparation consisted of intravenous aminophylline and subcutaneous epinephrine. The procedure is best avoided during acute bronchitis or acute exacerbations of chronic suppurative bronchitis complicating asthma. Maloney[209] pointed out that, when necessary, bronchoscopy can be done without removing the patient from his bed. Bronchostenosis was found to complicate asthma in about 40 per cent of patients, according to Moersch,[236] and of these, 68 per cent were better after bronchoscopy. There is no way to detect these patients in advance of the bronchoscopy. However, the procedure may be hazardous in the severe case of asthma. Léger[197] noted that bronchoscopic aspiration may be life saving and may prevent the development of atelectasis. Thomas[344] suggested that a local anesthetic not be used, because of the risk of fatal reactions. In children, the relief afforded, according to Crump,[63] is almost always immediate and dramatic, but is of course only temporary. However, Levin[201] has never found it necessary in children, if adequately treated, but granted that it may be required in the presence of severe bronchial plugging.

Minor[232] estimated that 75 per cent of asthmatic patients evince moderate to marked relief from bronchoscopic aspiration, although occasionally the wheezing may be worse for a few hours. Bronchial stenosis is thought to be uncommon. The indications for therapeutic bronchoscopy in asthma are given as the prevention of asphyxia, the termination of a chronic attack, the relief of atelectasis, and, in the rare instances where strictures are found, their dilatation.

Both Minor[232] and Bernstein and Klotz[26] have found that nasotracheal or pharyngolaryngeal aspiration by means of a soft rubber catheter may be helpful. While much of the secretions is beyond the range of the catheter, the suction gives appreciable stimulus and assistance in expelling the mucus. The cough induced may dislodge the secretions below, and some may eventually be brought within range of the catheter tip. This simple procedure may be a valuable aid to the tiring patient in a paroxysm.

TREATMENT: PNEUMOPERITONEUM

Banyai and Hirsh[18] stated that the aim of pneumoperitoneum in the treatment of hypertrophic (or as they prefer, "pseudohypertrophic") pulmonary emphysema is the restoration of the anatomic and physiologic status of the diaphragm. Relatively small amounts of air (500 to 600 cc at weekly intervals) as compared to those used in treating pulmonary tuberculosis seem to be most beneficial; increased mobility of the diaphragm has been demonstrated. Some patients also require an abdominal support. Some difficulty is encountered in deciding when to discontinue therapy. Pneumoperitoneum is not the complete management of emphysema, and the circulatory and bronchial disturbances which are part of the disease must also be corrected. Gratifying results are obtained in the great majority of patients.

Zak and Southwell[380] assessed the value of artificial pneumoperitoneum in the treatment of emphysema in ten patients, all but one of whom had chronic bronchitis and an asthmatic component. After the pneumoperitoneum had been established, weekly refills were given for periods of six to thirty months in amounts of 300 to 500 cc. Larger amounts may cause pleuritic pain and may even influence the respiratory mechanics adversely. Most of the pulmonary function studies were significantly improved, except in three severe long-standing cases, and x-ray revealed a higher resting level and a more advantageous expiratory position of the diaphragm. In six of seven moderately severe cases, subjective benefit was claimed by the patients, particularly with respect to exercise tolerance. It was concluded that a trial of artificial pneumoperitoneum is warranted in patients with moderate emphysema, especially below forty years of age.

According to Heilig, Mital and Sharma,[152] pulmonary emphysema and its consequence, chronic cor pulmonale, often develop in persons living in the near-desert region of Jaipur, India, because of the frequency of allergic bronchitis and asthma there, along with irritation of the respiratory passages by sand in the air, the occurrence of respiratory infections at the onset of the cold season, hard manual work, and other factors. Twelve cases of far-advanced emphysema, many of them with chronic pulmonary heart disease, were treated exclusively by means of pneumoperitoneum. Only one failed to do well. Electrocardiograms revealed a considerable lessening of right ventricular strain, venous pressures were greatly reduced, and the vital capacities increased 20 to 90 per cent. Control cases given either orthodox or placebo therapy and rest, did not do as well. The presence of congestive heart failure in emphysema, contrary to previous opinions, was apparently not a sound contraindication to pneumoperitoneum. Of course, other established methods of therapy should ordinarily be employed simultaneously. An Editorial[79] adds that unfortunately there are no criteria for predicting which cases of emphysema will actually benefit from pneumoperitoneum.

TREATMENT: PHARMACOTHERAPY

Oral and injectable medications have long been a mainstay of the therapy of asthma. Much of the recent literature constitutes a search for new and more effective remedies or for new modes of administration of older drugs. All of the references mentioned in the first section on Treatment naturally discuss the established medications. Solomon[323] has also examined the drug therapy of bronchial asthma. Among other comments, he suggested that should repeated injections of epinephrine fail to control the attack, the simultaneous injection of 0.5 ml of pituitrin may be effective. It is also noted that a particular treatment or drug may not always be continued indefinitely with full effectiveness and, accordingly, the therapy of each case should be frequently reviewed. Once the patient begins to feel that the practitioner has exhausted the remedies at his disposal or has ceased to maintain an alert interest in his condition, the attacks are likely to return with increasing severity and frequency. Despite this, there are few chronic conditions which will so richly reward a constant, vigilant, enthusiastic and encouraging attitude, and perseverance despite many disappointments.

Some of the drugs discussed below are also administered by aerosol, and the results of that technique are covered in a previous section.

Adrenergic Agents.—Despite the fact that epinephrine has been in use for more than two generations, opinions still differ regarding the proper dosage for the relief of a paroxysm of asthma. The extremes may be represented by the recent recommendations[55,283] of the subcutaneous injection of 1 to 2 minims a minute until bronchospasm decreases or until side effects become too severe, on the one hand, and of a single dose of 1.2 ml (20 minims) of the 1:1,000 dilution on the other. Robertson and Sinclair[283] add that many allegedly resistant cases have been due to too small a dose, but the reviewer has been impressed with the tachycardia, tremor and other signs of epinephrine overdosage in many of the "resistant" cases he has been called upon to see. Nevertheless, epinephrine is, in the absence of contraindications, generally agreed upon as the drug of choice to control acute paroxysms. Engelsher[87] has even suggested that concomitant hypertension or cardiac disease is not a contraindication to epinephrine if it is injected in a dose of 4 minims; an additional 2 to 4 minims may be given twenty to thirty minutes later, if necessary. Sheldon, Lovell and Mathews[318] enjoin caution in the exhibition of epinephrine in the aged, particularly those with hypertension, cardiac arrhythmia, or coronary artery disease. Isopropylarterenol given sublingually or by aerosol is not so likely to cause cardiovascular side effects.

Edwards[84] employed a sublingual tablet containing 10 mg of isopropylarterenol and 100 mg of benzyl nicotinamide sublingually, up to a maximum of three tablets in twenty-four hours. Children received one-half or less. The results were not startling, but were considered gratifying, even in patients who were intolerant of epinephrine. Less satisfactory results were obtained in children, probably because they did not use the tablets properly. Grant[132] observed a patient who acquired a persistent, widespread stomatitis after two months' sublingual use of isopropylarterenol (Isoprenaline sulfate). Repeated trial and withdrawal of the drug proved that it was the cause.

Commercial epinephrine solutions vary in their content of norepinephrine, although it usually constitutes less than 10 per cent, and this affects their relative bronchodilator and vasopressor effects. Lu and Allmark[205] devised a reliable tracheal chain method for the biologic assay of the comparative bronchodilator action of medications. Norepinephrine was found by this method to possess 5 to 10.3 per cent of the bronchodilator activity of epinephrine, and aminophylline only 0.054 per cent as much. The clinical efficacy of the theophylline drugs apparently requires pharmacologic clarification.

Theophylline Derivatives.—A new xanthine drug, choline theophyllinate (Choledyl®) was found to be stable, highly soluble, and less toxic than aminophylline (theophylline ethylenediamine). According to Dann,[65] Gagliani,[116] and their co-workers, ingestion of the drug produces significantly higher theophylline blood levels than comparable amounts of aminophylline with or without added aluminum hydroxide, and causes gastrointestinal irritation much less frequently. The same investigators[64,65,191] reported that choline theophyllinate was quite effective and well tolerated in a series of asthma cases when given in doses of 200 mg four times daily and, in some instances, in larger doses up to 1 gram four times a day. The vital capacity and maximum breathing capacity showed good responses in most cases. Katz and McCormick[180] observed benefit in 88 per cent of fifty patients with bronchospasm due to asthma or chronic pulmonary emphysema who were given 100 to 200 mg of the drug four times daily. There was reduced need for aerosol bronchodilators and only infrequent development of "fastness" to the drug during prolonged administration. The results were better prophylactically than when the drug was given after symptoms appeared, and also in the less severe cases, although intravenous choline theophyllinate may be used for acute severe bronchospasm. It is also said to be effective in rectal suppositories in chronic cases. Brown and Clancy[40] advanced an explanation of the inconstant effect of choline theophyllinate in their experience and as reported in the literature. On analysis, they noted the best results in cases of nonallergic infectious asthma in the older age group, usually with complicating bronchitis or emphysema. The responses were less favorable in paroxysmal allergic bronchial asthma.

Salomon et al[297] studied a chemical compound formed from unimolecular equivalents of theophylline and Orthoxine, a sympathomimetic drug. Orthoxine-theophylline was effective in intravenous doses of 250 to 300 mg in acute bronchospasm, and by continuous intravenous drip in doses of 0.5 gram in 1,000 cc of dextrose solution every eight hours in terminating status asthmaticus in ten cases, including five that had failed to improve after intravenous aminophylline. It was also effective by aerosol. Oral administration proved promising in mild, chronic asthma. Side reactions were more frequent than with a comparable dose of aminophylline, but were of the same general nature. In brief, the new drug was considered equal to and in some instances superior to aminophylline.

The toxicity of aminophylline, particularly in children, has recently been emphasized. Rounds[295] reported six children, one to three years of age, who manifested varying combinations of central nervous system stimulation, vascular phenomena, vomiting, and renal manifestations after amino-

phylline in rectal suppositories or intravenously. One patient died of respiratory paralysis. It was felt that the usually recommeded dosage in children may actually be excessive. Individual idiosyncrasy did not seem to be a prominent factor. Pioppi[257] observed two cases of severe generalized reactions to aminophylline rectal suppositories in children two and three years old; one died and autopsy revealed no major abnormalities. In answer to his query, it was pointed out that allergy to benzocaine or to the suppository base must be considered, but that aminophylline toxicity was probably responsible. Caution in pediatric dosage was again advocated. Levin[201] also warned against overdosage; in addition to frequent nausea and vomiting, he has seen several children with peripheral vascular collapse from aminophylline.

Antihistaminic Drugs.—With some qualifications, opinions generally continue unfavorable to the use of antihistaminics in asthma. Bowen[88] felt that they are contraindicated because of their atropine-like action. Farrar[89] agreed in principle, but noted that 20 to 40 per cent of patients are reported in the literature as showing some improvement, although more so with regard to coughing than wheezing. Evening doses may prevent nocturnal paroxysms. Aerosol is more effective than oral administration, but is irritating to an already inflamed mucosa. In epinephrine-refractory status asthmaticus a single intravenous injection, given cautiously, may be helpful. Thomas[344] noted that antihistaminics are sometimes temporarily of value, then lose their effectiveness and seem to cause more harm than good. On occasion, intramuscular or intravenous injections are beneficial, particularly in asthma resulting from drug or serum reactions. Bernstein and Klotz[26] stated that these drugs have little place in treating acute asthma except when the secretions are predominantly "wet"; under these circumstances, their drying and sedative effect may be beneficial. Walther[371] recorded good results from antihistaminics in pollen asthma in children, and the answer to a query[268] favors their use in nonseasonal pediatric asthma.

Several reports referred to single antihistaminic drugs. Mulligan[243] observed that when asthma complicated hay fever, treatment with a sustained-release form of chlorprophenpyridamine (Teldrin spansules®) benefited chiefly the nasal symptoms; although the patients were made more comfortable, it was doubted that the asthma was relieved to any extent. Green,[133] using the same preparation, found that allergic reactions superimposed on bronchial asthmatic conditions responded, but the asthma itself was for the most part unaffected. Some patients, however, contended that their wheezing had been reduced. Rogers[287] reported somewhat more favorable results with the same product, only a small proportion of patients not being helped. Clistine® maleate in doses of 4 or 6 mg gave no relief to one case of asthma, but afforded considerable relief in twenty-six patients with both allergic rhinitis and asthma, according to Beale, Rawling and Figley.[21] The last two articles do not specify which of the symptoms were benefited in patients with more than one diagnosis. According to Arbesman,[8] Vibazine, a new antihistaminic, was ineffective in asthma, and while alleviating nasal symptoms in 30 per cent of cases of seasonal hay fever with associated asthma, influenced the bronchial symptoms in only 3 per cent. Kaplan et al[177] and Dutton and Halpin[77] observed no benefit in asthma from a new drug called FC-1 (tropin-4-

chlorbenzhydryl ether hydrochloride), although Dutton claimed some results in seasonal asthma complicating hay fever, especially in children.

Halpern's[145] explanation for the lack of effectiveness of antihistaminic drugs in asthma was referred to in the section on Pathology.

Brown[39] and Farrar[89] noted that bronchial asthma may actually ensue from antihistaminic treatment of hay fever or urticaria. The former alluded to Pellerat's hypothesis that the skin cells containing excessive histamine may "fix" the antihistaminic agent; the free blood histamine levels may then increase to a point at which the bronchioles, originally less susceptible than the skin, are exposed to quantities beyond the resources of their own histaminolytic protection. In a four-year period, Macaulay[207] saw nine cases, among 3,000 patients with hay fever and allergic rhinitis, in whom the administration of antihistaminics appeared to induce asthma. In each instance the drug relieved the nasal symptoms coincidentally with the appearance of the asthma. No one antihistaminic appeared particularly culpable. The asthmatic state was, in most instances, readily reversible upon discontinuance of the drug, the patient being restored to his previous status. It was postulated that the antihistaminic was given in sufficient dosage to counteract the effects of the allergen-reagin reaction in one tissue, but that the reaction appeared in another tissue which the dosage administered was inadequate to protect, the H-substance having been released in a more inaccessible fashion.

Chlorpromazine.—Chlorpromazine, a phenothiazine derivative, known as Thorazine,® and in other countries as Largactil,® Megaphen,® or Ampliactil,® has been used in various neuropsychiatric disorders, nausea and vomiting of diverse causes, and many other conditions. Three reports from abroad, each claiming priority in the field, described its employment in asthma. Galup[118] noted that while antihistaminic drugs are not generally useful in asthma, three phenothiazine derivatives, although having different pharmacologic actions, may be of value. Promethazine (Phenergan®), essentially an antihistamine, has an inconstant and unpredictable effect in asthma, but may be worth trying. Some feel that it helps in the milder episodes, but is contraindicated in the severer ones, and may aggravate crises. Multergan, a quaternary ammonium compound having both antihistaminic and anticholinergic action, is, in an inconstant way, sometimes superior to Phenergan in asthmatic attacks—especially when vasomotor abnormalities or bronchial hypersecretion are prominent. Galup administered 25 mg of chlorpromazine intramuscularly in a patient in severe status asthmaticus in whom sympathomimetic drugs had been overused and theophylline derivatives were ineffective, and who seemed moribund. The effects were immediate and the chlorpromazine was considered life-saving. The mechanism was thought to be an autonomic nervous system blockade, plus perhaps a direct spasmolytic action. Oral use for more or less prolonged periods in selected cases was suggested. Perpère[255] employed 25 to 30 mg intramuscularly, usually at bedtime, and noted favorable results. Often a single dose sufficed, as though a cycle had been interrupted.

Robinson and Zuck[285] stated that chlorpromazine has a depressant effect on the cerebral cortex but not on the respiratory center. Laryngeal and tracheobronchial reflexes mediated by the vagus nerve are depressed;

animal experiments revealed a reduction in capillary permeability, reduction of mucous membrane edema, and a lowering of the basal metabolic rate. Slow intravenous injections of 6 to 25 mg of chlorpromazine were given to four patients with severe asthma. Promethazine (Phenergan) and pethidine (Dolantin®) were usually given at the same time. The last two drugs may have been of some value, but most of the improvement was attributed to the chlorpromazine which enabled the patient to sleep without depressing respiration. Relief of bronchospasm was not immediate and may have resulted more from sedation than from any direct antispasmodic action. After the injection, sweating ceased, cyanosis was lessened, and the extremities became warmer. Although tachycardia regularly ensued, the rhythm remained regular, and the fall in blood pressure was only slight and transient. It was suggested that parenteral chlorpromazine should be restricted to the more severe cases of asthma.

More recently, Ende[86] administered chlorpromazine intramuscularly to twelve cases of severe asthma, some receiving 25 mg every four hours, others a single dose of 25 or 50 mg. All were on bed rest. All but one patient improved. In one case the medication was considered to be life saving. The improvement was noted in forty-five minutes to one hour after the injection. The drug was of value in alleviating the anxiety associated with the paroxysms. Repeated physical examinations did not show any lessening of the wheezing after chlorpromazine. The only side effects were superficial ulcerations in three patients to whom the injections were not given sufficiently deeply. The drug was considered a safe nonaddicting sedative of considerable value in the treatment of asthma.

Single cases were treated by Norpoth, Flacke and Clösges[247] and Moyer et al.[242] In a case resistant to other medications, the former obtained the first favorable response after giving 25 mg of chlorpromazine intramuscularly. Further improvement followed oral administration in conjunction with phenobarbital. In a pregnant woman in the second trimester, Moyer et al[242] were able to terminate attacks of status asthmaticus within thirty minutes on three different occasions by injections of 50 mg of chlorpromazine. The condition had yielded only slowly to previous therapy with epinephrine, intravenous aminophylline and other measures.

Steigman and Vallbona[327] found chlorpromazine useful as an antiemetic to control the vomiting caused in children by a wide variety of nonalimentary conditions. including bronchial asthma.

Parasympathetic Blocking Agents.—A new anticholinergic drug, Antrenyl® (diethyl [2-hydroxyethyl] methylammonium bromide α-phenylcyclohexane glycolate) in intravenous dosage of 1.0 mg significantly improved the vital capacity, maximum breathing capacity, volume of deep respiration, and the breathing reserve in a series of seventeen cases of intrinsic asthma or hypertrophic pulmonary emphysema with associated bronchospasm, according to Leslie, Dantes and Rosove.[199] By comparison, intravenous aminophylline caused less striking increases, while Paveril® phosphate (a papaverine analogue) and a new adrenergic drug were without significant effect. While the subjective improvement, on the whole, was greater and more prolonged after Antrenyl than after aminophylline, this was offset by an unpleasant dryness of the mouth in many patients, and by difficulty in urination in some. Because of its suppression of bronchial secretions, the drug should probably not be used in ordinary bronchial asthma but reserved for bronchospastic conditions associated

with the production of considerable sputum. The administration of Antrenyl by aerosol was considered above.

In eleven cases with emphysema and/or asthma, Sjoerdsma and Dodge[321] found that 50 mg of methantheline bromide (Banthine®) intravenously produced a considerable increase in the pulmonary function in eight instances, although only one case approached a normal ventilatory pattern. Symptomatic improvement corresponded with the results of the ventilatory tests. Some side effects such as tachycardia, dryness of the mouth and blurring of vision, occurred uniformly, but were not severe enough to interdict the use of the drug; one patient with benign prostatic hypertrophy was troubled by urinary retention. It was concluded that further trial of the drug as an adjunct in the therapy of asthma and emphysema is warranted.

According to Frank and MacLaren,[104] "medical vagotomy" by the oral administration four times daily of 50 to 100 or even 200 mg of Prantal,® a quaternary ammonium derivative with anticholinergic effects, was almost uniformly disappointing in the symptomatic relief of asthma. Previous reports noted wide variations with respect to the observed results. Interestingly, nasal allergies were benefited to some extent.

Iodides.—Salts of iodine have been employed in the treatment of asthma for over a century, as witnessed by the reprinting of a historical document[51] from 1845. The value of potassium iodide in this disease is said to have been discovered accidentally by a Professor Mutter of Philadelphia. It is interesting to note that "severe attacks of catarrh, or . . . errors in diet" were recognized even then as causing relapses. Allergists are still wrestling with these problems as several articles referred to in this review attest. Such complications of iodide therapy as skin eruptions and conjunctivitis were acknowledged. Some 109 years later, Cope[61] reported a case of iodine intoxication manifested by a severe fungating iododerma of the face and elsewhere, extreme eosinophilia (66 per cent of a leukocyte count of 32,950 per cu mm), and marked toxicity. The patient had had a transitory reaction to an iodine-containing contrast medium employed in intravenous pyelography some months before, but had taken potassium iodide after prostatectomy to avoid fibrous contraction of the prostatic bed, without untoward effects. Two months later, when he took proprietary asthma tablets containing potassium iodide, the iododerma appeared. There was thus a "rest period" without the medication, as is so often seen in drug sensitivity.

Morgans and Trotter[237] reported two instances of myxedema attributed to iodide administration and claimed they were the first such cases to be recorded. One was in a chronic asthmatic who had taken an asthma mixture containing 7½ grains of sodium iodide (equivalent to 423 mg of iodine) at least every four hours for four years. A goiter and clinical and laboratory evidence of hypothyroidism developed. When the medication was discontinued a temporary thyrotoxicosis appeared. The same asthma mixture but with the sodium iodide omitted was administered later, but status asthmaticus intervened. Iodides were again given, and thyroid enlargement recurred. The authors discussed the possible reasons why patients taking iodide do not usually have thyroid disturbances. Certainly the euthyroid asthmatic patient almost always tolerates iodides. Bell[24] had earlier reported five patients who developed myxedema or goiter or both while on prolonged iodide therapy for asthma. He and Byrd recently

added[24] a case of hyperthyroidism with exophthalmos and goiter, developing after thirty-two months of treatment with potassium iodide. Laboratory findings were of course influenced by the medication. It was not considered likely that the iodide therapy was responsible for the development of the thyrotoxicosis.

Morphine and Demerol.—Opinions still continue unfavorable to the use of morphine in asthma.[17,26,154,233,286] Rodbard[286] attributed its deleterious and occasionally fatal effects to its action in increasing bronchomotor tone, causing alveolar air entrapment and paving the way to asphyxia, rather than to its depressant action on the respiratory center. Mitchell and DeJong[233] conducted a review of the fatalities from asthma at the Montreal General Hospital, prior to the discontinuance of the use of the drug in such cases, and showed that a high proportion of the patients had received morphine or Demerol shortly before death. Using bronchial muscle preparations from nonallergic human beings and from dogs, they found that the addition of morphine to the water-bath in concentrations up to 10 mg per 100 ml had no relaxing or stimulating effect on bronchial muscle. However, the presence of morphine potentiated the contractile effect of acteylcholine on the smooth muscle. These findings tend to support the idea that the adverse effect of morphine in asthma may be related to an inhibitive effect of the drug on cholinesterase, as has been previously reported by others.

Meperidine or isonipecaine hydrochloride (Demerol) may be used in asthma under close supervision, according to Bernstein and Klotz.[26] Banyai[17] grants that it alleviates and prevents asthmatic paroxysms when taken orally at required intervals, but does not recommend it because its absorption from the intestinal tract is not uniform and because it is habit forming, leading to abuses. Parenthetically, intramuscular injection is preferred for parenteral use, since prolonged subcutaneous administration may be locally irritating. That meperidine addiction is not an academic problem was emphasized by Rasor and Crecraft.[274] Of several hundred meperidine addicts admitted to the U. S. Public Health Service Hospital at Lexington, Kentucky, a significant percentage had acquired the addiction because of asthma.

Herschfus et al[154] consider Demerol, in proper dosage, a useful and safe drug in the treatment of an acute asthmatic attack or of status asthmaticus when the usual methods of treatment have failed or fastness to epinephrine or aminophylline has developed. The drug was shown to have good anticholinergic and fair antihistaminic action. Pulmonary function studies before and after the subcutaneous administration of 50 to 100 mg of Demerol in fourteen patients with acute asthma demonstrated diminished hyperventilation in all the patients, and an increase of the vital capacity and maximum breathing capacity in most. Subjectively, all patients felt slightly to greatly relieved. Mild side effects, chiefly dizziness, sleepiness, nausea or vomiting, occurred in several cases.

Other Preparations.—Nitrogen mustard was administered intravenously in doses of 2.5 mg to a patient with severe asthma by Arya.[12] Despite the resultant vomiting, improvement followed in a few hours. After a total of four injections on alternate days, the patient was completely asymptomatic for months. The results were also encouraging in three other chronic cases.

Prolonged sleep for eighteen to twenty hours each day for two to three weeks was induced with Amytal® by Gallini[117] in the treatment of five cases of severe status asthmaticus not responding to other therapy, including cortisone and intravenous aminophylline. Varying doses of 0.6 to 1 gram of Amytal per day were required. Penicillin and oxygen were also administered, but no other drugs, except epinephrine when needed. The results were excellent, and remissions lasted for months. Retreatment of two patients about one year later was not as successful.

Since tyrosine is one of the precursors of epinephrine, and a phosphorylated derivative of pyridoxine acts as a necessary coenzyme in the conversion, while nicotinamide has antihistaminic properties, Woodard[379] employed tablets containing 200 mg of tyrosine, 2.5 mg of pyridoxine, and 10 mg of nicotinamide. Adults received two to eight tablets four times daily, children less. Favorable results were claimed in 88 per cent of thirty-four patients so treated, including two cases of status asthmaticus refractory to epinephrine and aminophylline.

An antimalarial quinoline compound, chemically modified to produce anticholinergic, antihistaminic, and bronchodilator properties and known as Aureoquin, was again reported by Geschickter[123] as very effective in the treatment of bronchial asthma. However, Kramis Tejeda[189] found that two months' therapy with atabrine produced no improvement in six patients with asthma, although helpful in certain types of dermatitis.

Hansen-Pruss[148,149] emphasized the potential toxicity of inorganic arsenic compounds in the treatment of asthma. Seventeen adults who had taken the "Gay treatment" or some modification of it for periods of from three weeks to over two years were seen at the Duke Hospital three weeks to three years after the last administration because "cure" had not materialized and in ten cases also because of some manifestation of poisoning with arsenic. The usual formula taken contained 8 ml of Fowler's solution (5 ml for children) in 60 ml of the mixture. Positive tests for arsenic in the hair occurred in fifteen of the seventeen cases, and abnormal urinary arsenic content in seven. In this series of cases, two patients had abnormal liver function studies, one had renal damage although the inorganic arsenic could not be absolutely proved culpable, three had skin eruptions, and nearly all had gastrointestinal complaints. The last usually began two to six weeks after treatment had been started. E. D. Gay[119,120] defended the "Gay treatment," alleging that certain of the reported cases of arsenic poisoning had not been treated by him or his associates, and that they had taken many times the amount of arsenic he had advocated. He admitted seeing an occasional arsenical reaction (but no more than six cases of serious arsenical damage in 1,000 cases), but denied that it constituted a serious threat to the merit of this treatment because of its early recognition. He promised a detailed account of the procedure and a statistical survey of 1,000 cases treated by him.

Reserpine (Serpasil®), a hypotensive agent and tranquilizer, was given orally by Segal and Attinger[310] to fifty-six patients with chronic asthma and pulmonary emphysema in doses of 0.1 to 0.25 mg three times daily over periods of two weeks to six months. All of them also received aminophylline and bronchodilator aerosols, and some, corticosteroids or corticotropin. Four patients noted lessening of dyspnea and twenty-two noted a sense of greater security and relaxation. The best effects were observed in patients having central nervous system effects from the other therapy, and in those with associated hypertension. Side effects seen in

twenty-two cases included fatigue, sleepiness, nasal obstruction, fullness or tightness in the chest, anorexia, and nausea. In a single patient, intravenous reserpine failed to afford protection against the bronchospastic effects of mecholyl, as would be anticipated from its cholinergic properties.

Vitamin C therapy of allergic diseases has given rise to contradictory opinions. McNally[219] blamed the failures on inadequate dosage and on the fact that vitamin C cannot be effective in the presence of gross infection or marked histamine activity. He recommended doses of 500 to 1,500 mg daily after infection has been controlled, and successfully treated five cases of asthma. He attributed the benefits to the effect on the intracellular ground substance, thus preventing abnormal absorption of the sensitizing agent by the mucous membrane, and also to improved resistance to respiratory tract infection. The effect of ascorbic acid on the circulating eosinophils was uncertain, but there seemed to be a downward trend.

Hesperidin given three times daily along with calcium lactate for one to two weeks was noted by Beiler[23] to have produced prolonged remissions in bronchial asthma.

The effects of fumes of burning papers saturated with potassium nitrate were, according to a century-old report,[246] attributed to the production of oxygen! Another reprinted old article[350] discussed the early use of fluid extract of euphorbia, and mentioned the existence of "Asthmatic Institutes" employing secret treatment methods over sixty years ago, as well as the recognition of the benefits to asthma sufferers of abstaining from tobacco.

TREATMENT: OTHER ASPECTS

A non-surgical method of interrupting the cervico-dorsal sympathetic chain and thereby part of the autonomic innervation of the lung was devised by Gianfranco.[124] About 0.5 ml of absolute alcohol was injected intrathecally between the sixth and seventh cervical vertebrae, the patient being so positioned as to allow the alcohol to rise to the posterior spinal radicles and the supine position being maintained for two hours. The procedure was carried out bilaterally. A sense of warmth in the region of the scapula was induced, followed by hyperesthesia or anesthesia, but untoward effects were negligible, except for fairly frequent headaches and one case of asceptic meningitis. Tried in fifty cases of resistant asthma, the method gave prompt relief in seventeen; none was made worse. The benefit correlated with the induced anesthesia. Relapses ensued in days or months in the successful cases. Aside from technical difficulties, treatment failures were attributed to arachnoidal adhesions and perhaps to the fact that insufficient nerves were interrupted.

Arnoldsson and Pipkorn[11] administered testosterone proprionate (10 mg daily for ten days) to twelve patients with asthma. Pretreatment determinations had shown abnormal blood proteins in nine of sixteen cases, characterized by a decreased serum albumin and increased α- and β-globulins. Under therapy the albumin increased and the α-globulins decreased, thoughly rarely to normal levels, in about half the cases, and the β-globulins sometimes fell. Clinical improvement did not entirely parallel the induced changes in the plasma protein fractions, but there appeared to be some trend in that direction.

Although details are not available, Golden[127] reported dramatic improvement (though slower than from epinephrine) and "permanent" benefit in acute bronchial asthma from one to three intramuscular injections of 2.5 mg of trypsin repeated daily as needed. In fourteen chronic cases

given two to twenty-two injections (average, seven) in the same dosage, all patients improved slowly over a period of five to fifteen days. Decreased cough and orthopnea were noted, and the duration of the relief was considered noteworthy. Sometimes local pain and induration occurred at the injection site. Regarding untoward effects from trypsin, both Fisher and Wilensky[95] and Slepian[322] showed that intradermal skin and passive transfer testing cannot be used as a guide in predicting constitutional reactions from parenteral trypsin administration.

Bowen[33] again referred to the benefits of gamma globulin therapy in certain asthmatic children, who, despite other therapy, have violent asthmatic attacks following respiratory infections during the winter months. Injections of 4 to 6 cc of gamma globulin every four weeks greatly reduced the bronchitis and asthma in a small group, particularly in comparison to a control group. Further trial of this method was suggested, as well as efforts to produce an even more effective gamma globulin preparation.

Wittich[377] employed a nasal spray (Biomydrin®), containing two antibiotics, a surface wetting agent, an antihistamine, and a topical vasoconstrictor, in a variety of respiratory allergies. In the chronic superimposed nasal infection which aggravated the asthma due to bacterial allergy or infection, there was a notable improvement of the asthma symptoms in some if the spray was used as infrequently as once or twice daily. In connection with topical nasal therapy, it is not out of place to call attention to the potential dangers of using tetrahydroxoline hydrochloride (Tyzine®) in children, as mentioned in two recent reports[107,136] from opposite sides of the country.

COMPLICATIONS

The common complications of asthma, according to Carryer et al,[49] are bronchitis, bronchostenosis, and pulmonary emphysema. Persistent suppresssion of breath sounds usually in the posterior or lateral portion of the lung bases, blood-tinged sputum (since hemoptysis is said not to occur in uncomplicated asthma) or the "sputum retention syndrome" suggest the possible presence of bronchostenosis. The sputum retention syndrome is characterized by the frequent occurrence of chills and fever, in an acute illness terminated by coughing and the expectoration of purulent sputum.

Hemoptysis.—Turiaf, Blanchon and Chabot[352] noted hemoptysis in 6 per cent of a series of 1,500 cases of asthma. It was never profuse. There was no correlation with age, sex, or type of asthma, but hemoptysis was more likely in disease of long standing. Investigation revealed a cause for the bleeding, other than asthma, such as tuberculosis, cardiac disease, or bronchiectasis, in about 15 per cent of the cases of "hemoptysic asthma." Bronchoscopy showed the usual asthmatic findings and occasionally a fragile bronchial mucosa. Bronchography revealed only a few instances of bronchiectasis or bronchostenosis. In general, the hemoptysis was blamed on increased capillary permeability resulting from neurovasomotor disturbances, possibly related to the vascular changes incident to a severe allergic state.

Bronchostenosis and Bronchiectasis.—Turiaf, Rose and Marland[358] described the finding in asthmatic patients not infrequently of more or less

twenty-two cases included fatigue, sleepiness, nasal obstruction, fullness or tightness in the chest, anorexia, and nausea. In a single patient, intravenous reserpine failed to afford protection against the bronchospastic effects of mecholyl, as would be anticipated from its cholinergic properties.

Vitamin C therapy of allergic diseases has given rise to contradictory opinions. McNally[219] blamed the failures on inadequate dosage and on the fact that vitamin C cannot be effective in the presence of gross infection or marked histamine activity. He recommended doses of 500 to 1,500 mg daily after infection has been controlled, and successfully treated five cases of asthma. He attributed the benefits to the effect on the intracellular ground substance, thus preventing abnormal absorption of the sensitizing agent by the mucous membrane, and also to improved resistance to respiratory tract infection. The effect of ascorbic acid on the circulating eosinophils was uncertain, but there seemed to be a downward trend.

Hesperidin given three times daily along with calcium lactate for one to two weeks was noted by Beiler[23] to have produced prolonged remissions in bronchial asthma.

The effects of fumes of burning papers saturated with potassium nitrate were, according to a century-old report,[246] attributed to the production of oxygen! Another reprinted old article[350] discussed the early use of fluid extract of euphorbia, and mentioned the existence of "Asthmatic Institutes" employing secret treatment methods over sixty years ago, as well as the recognition of the benefits to asthma sufferers of abstaining from tobacco.

TREATMENT: OTHER ASPECTS

A non-surgical method of interrupting the cervico-dorsal sympathetic chain and thereby part of the autonomic innervation of the lung was devised by Gianfranco.[124] About 0.5 ml of absolute alcohol was injected intrathecally between the sixth and seventh cervical vertebrae, the patient being so positioned as to allow the alcohol to rise to the posterior spinal radicles and the supine position being maintained for two hours. The procedure was carried out bilaterally. A sense of warmth in the region of the scapula was induced, followed by hyperesthesia or anesthesia, but untoward effects were negligible, except for fairly frequent headaches and one case of asceptic meningitis. Tried in fifty cases of resistant asthma, the method gave prompt relief in seventeen; none was made worse. The benefit correlated with the induced anesthesia. Relapses ensued in days or months in the successful cases. Aside from technical difficulties, treatment failures were attributed to arachnoidal adhesions and perhaps to the fact that insufficient nerves were interrupted.

Arnoldsson and Pipkorn[11] administered testosterone proprionate (10 mg daily for ten days) to twelve patients with asthma. Pretreatment determinations had shown abnormal blood proteins in nine of sixteen cases, characterized by a decreased serum albumin and increased α- and β-globulins. Under therapy the albumin increased and the α-globulins decreased, thoughly rarely to normal levels, in about half the cases, and the β-globulins sometimes fell. Clinical improvement did not entirely parallel the induced changes in the plasma protein fractions, but there appeared to be some trend in that direction.

Although details are not available, Golden[127] reported dramatic improvement (though slower than from epinephrine) and "permanent" benefit in acute bronchial asthma from one to three intramuscular injections of 2.5 mg of trypsin repeated daily as needed. In fourteen chronic cases

given two to twenty-two injections (average, seven) in the same dosage, all patients improved slowly over a period of five to fifteen days. Decreased cough and orthopnea were noted, and the duration of the relief was considered noteworthy. Sometimes local pain and induration occurred at the injection site. Regarding untoward effects from trypsin, both Fisher and Wilensky[95] and Slepian[322] showed that intradermal skin and passive transfer testing cannot be used as a guide in predicting constitutional reactions from parenteral trypsin administration.

Bowen[33] again referred to the benefits of gamma globulin therapy in certain asthmatic children, who, despite other therapy, have violent asthmatic attacks following respiratory infections during the winter months. Injections of 4 to 6 cc of gamma globulin every four weeks greatly reduced the bronchitis and asthma in a small group, particularly in comparison to a control group. Further trial of this method was suggested, as well as efforts to produce an even more effective gamma globulin preparation.

Wittich[377] employed a nasal spray (Biomydrin®), containing two antibiotics, a surface wetting agent, an antihistamine, and a topical vasoconstrictor, in a variety of respiratory allergies. In the chronic superimposed nasal infection which aggravated the asthma due to bacterial allergy or infection, there was a notable improvement of the asthma symptoms in some if the spray was used as infrequently as once or twice daily. In connection with topical nasal therapy, it is not out of place to call attention to the potential dangers of using tetrahydroxoline hydrochloride (Tyzine®) in children, as mentioned in two recent reports[107,136] from opposite sides of the country.

COMPLICATIONS

The common complications of asthma, according to Carryer et al,[49] are bronchitis, bronchostenosis, and pulmonary emphysema. Persistent suppresssion of breath sounds usually in the posterior or lateral portion of the lung bases, blood-tinged sputum (since hemoptysis is said not to occur in uncomplicated asthma) or the "sputum retention syndrome" suggest the possible presence of bronchostenosis. The sputum retention syndrome is characterized by the frequent occurrence of chills and fever, in an acute illness terminated by coughing and the expectoration of purulent sputum.

Hemoptysis.—Turiaf, Blanchon and Chabot[352] noted hemoptysis in 6 per cent of a series of 1,500 cases of asthma. It was never profuse. There was no correlation with age, sex, or type of asthma, but hemoptysis was more likely in disease of long standing. Investigation revealed a cause for the bleeding, other than asthma, such as tuberculosis, cardiac disease, or bronchiectasis, in about 15 per cent of the cases of "hemoptysic asthma." Bronchoscopy showed the usual asthmatic findings and occasionally a fragile bronchial mucosa. Bronchography revealed only a few instances of bronchiectasis or bronchostenosis. In general, the hemoptysis was blamed on increased capillary permeability resulting from neurovasomotor disturbances, possibly related to the vascular changes incident to a severe allergic state.

Bronchostenosis and Bronchiectasis.—Turiaf, Rose and Marland[358] described the finding in asthmatic patients not infrequently of more or less

pronounced narrowing of the segmental bronchi and also marked stenosis of the lower bronchi, as evidenced by bronchography and bronchoscopy. The first portion of the lower lobe bronchus is the usual site of involvement, sometimes bilaterally, and less often the upper lobe bronchus. The pathogenesis involves an inflammatory reaction, hypersecretion, spastic stenosis, and hypertrophy of the bronchial musculature. Greening and Atkins[185] made very similar observations of a consistent abrupt narrowing of the bronchi shortly after their origin from the main trunks, and referred to the condition as bronchial attenuation. Their patients fell into three clinical groups: those with diffuse pulmonary emphysema, those with asthma or asthmatic bronchitis and hypersensitivity states, and a less well defined group with features suggestive of bronchiectasis. Such attenuation was almost always present in asthma and emphysema. It seemed to be reversible in its early stages, but may become irreversible if long continued. The three groups presented differential bronchoscopic findings.

An editorial[80] discussed bronchostenosis as a complication of asthma. Cough is the commonest symptom, the quantity of sputum being variable. Hemoptysis occurs in about one-third of the cases, fever and chills not uncommonly. A clinical diagnosis of pneumonia is often made. Persistent or unilateral physical signs, and rapid change of findings are suggestive. The chest roentgenogram suggests a localized atelectasis or, less often, bronchiestasis. The most common indication for bronchoscopy in patients with asthma is claimed to be the need for confirming or excluding the diagnosis of bronchostenosis.

According to Marland and Blanchon,[212] bronchial dilatations occurring in persons with asthma are always multiple and usually bilateral. The enlargement in calibre is usually moderate, and so better termed a distention rather than a dilatation. It may be moniliform or cylindrical, rarely saccular, in type. Stenotic areas are often associated with the dilatation—sometimes even in the same bronchus. The etiology is not clear, but the condition is more likely to occur in "late" asthma. The treatment is essentially that of the asthma, plus bronchoscopic drainage and systemic antibiotics. Stellate ganglion block and surgical excision are sometimes advised.

Pittman[258] remarked that bronchiectasis in older people (over forty years of age) differs in nature and prognosis from that in the younger age group. As a rule, it is secondary to pulmonary fibrosis which itself may be associated with emphysema, endobronchial or fibrotic tuberculosis, or long-standing asthma.

Emphysema.—A number of notations pertinent to the subject of pulmonary emphysema as a complication of asthma have, of necessity, been included in previous sections, particularly those on Pulmonary Function Tests and on Treatment. Banyai[16] prefers the term "pseudohypertrophic emphysema" to the adjectives hypertrophic, genuine, idiopathic, diffuse vesicular, or destructive. Boyer and Ramsay[34] discussed the roentgen diagnosis of emphysema. Since the best evidence is based on both flattening and decreased diaphragmatic mobility, either fluoroscopy or inspiratory-expiratory films are necessary. A unilateral form of emphysema characterized by unequal transradiancy of the lungs must be differentiated.[7]

The management of pulmonary emphysema has been recently discussed by Gordon,[129] Banyai,[16] Miller and Helmholz,[230] and Segal et al,[312,313] and of emphysema in the aged by Hansen-Pruss and Charlton.[150]

Two cases of subcutaneous emphysema complicating asthma, one of them with severe signs of mediastinal airblock, were contributed by Lass and Heyman.[195]

Cor Pulmonale.—Turiaf and Thin[359] studied the cardiovascular changes occurring in the course of severe status asthmaticus. The most consistent findings were sinus tachycardia, engorgement of the cervical veins, moderate hepatomegaly, and cyanosis. By x-ray, a decrease in the size of the cardiac silhouette and retraction of the descending arch of the aorta were often seen. Electrocardiography showed a marked increase in the height of P_2 and P_3 and clockwise rotation of the heart with the appearance of S-waves in the precordial leads. These findings during status asthmaticus must not be interpreted as true acute cor pulmonale. They result from a shift in the cardiac axis and changes in the intrapulmonary pressure relationships, and are in themselves not of serious prognostic significance. When the status asthmaticus is controlled by therapy, the cardiac signs usually disappear rapidly. The prognostic signs with regard to cardiac involvement are the intensity of the tachycardia, the duration of the attack and the degree of anoxia, and particularly the myocardial status prior to the attack.

Segal, Radovsky and Salomon[311] discussed the diagnosis and treatment of chronic cor pulmonale. Once developed, it is treated similarly to any heart failure except for special attention to the underlying etiologic disorder, particularly the associated bronchoconstriction and infection. Although the value of digitalis has been questioned, it is now considered essential, along with salt restriction and diuretics.

Dussert[76] treated thirty-two cases of cor pulmonale complicating bronchial asthma by an aerosol of dihydroxypropyl-theophylline combined with an albumin-free water-soluble myocardial extract from freshly slaughtered animals. Promising results were obtained. The preparation was less effective by injection. The rationale was not too clear, except that the combination seemed to possess marked bronchodilator properties.

Other Complications.—Two instances of *rupture of the esophagus* during status asthmaticus were reported by Mitchell et al.[234] These are claimed to be the first such cases in the literature. Asthma was responsible for the accident to the extent that it caused severe vomiting. Both occurred in the distal portion of the esophagus and autopsy revealed a suspicion of pre-existing disease of the esophagus in only one. The complex clinical picture of this interesting condition included mediastinitis, subcutaneous emphysema, pleural effusion, hydrothorax or hydropneumothorax, and shock. The condition is uniformly fatal if not promptly operated on, and even with surgery only two-thirds survive.

Stewart, Wray and Hall[329] observed two asthma patients in whom an unusual prostatic lesion, consisting of focal granulomata with central fibrinoid necrosis resembling the lesions of periarteritis nodosa, was found. One patient also showed severe focal and diffuse eosinophilic infiltrations in the prostatic tissue and eosinophilic pus in the prostatic glands. The picture was comparable, apart from topographic considerations, to Löffler's syndrome and was called *allergic prostatitis.* Three similar cases in the literature had been labelled allergic granulomas of the prostate gland or granulomatous prostatitis. The condition must be rare,

but it is suggested that in asthma patients developing prostatic symptoms the urine be examined for eosinophils before and after prostatic massage.

Foley and Paterson[97] reported *neurologic complications* in a case of status asthmaticus in the course of which a two- to four-minute period of apnea occurred, accompanied by a convulsion. Stupor, cortical blindness, athetosis, spastic quadriplegia, and cerebellar ataxia followed, and most of these findings persisted.

A follow-up of seventy-eight patients who had been hospitalized for *infantile eczema* revealed that 50 per cent of them subsequently developed bronchial asthma, as compared to 2 per cent in control groups, according to Vowles et al.[367] It may be noted that the incidence of later recurrent bronchitis, hay fever, pneumonia, migraine, and urticaria also exceeded by far that in the controls.

Mayer[217] suggested research into the problem of the *alternation of allergic manifestations* in the same patient, as exemplified by neurodermatitis and bronchial asthma. The best example is multiple allergy to the dye paraphenylenediamine. Starting as a neurodermatitis, sometimes preceded by a contact dermatitis due to the same allergen, the subsequent asthma may alternate with the atopic dermatitis. Other examples are cited. Such a double allergic state may occur when different receptor systems become sensitized to the same allergen or when the patient becomes simultaneously or successively sensitized to two or more different compounds.

Thirty-one patients with both bronchial asthma and a *peptic ulcer* were observed by Jacquelin et al.[171] In eighteen instances the asthma had been present before the ulcer, and in thirteen, the opposite was true. Males predominated by a ratio of 3.5:1. Marked hereditary factors were detected with respect to both diseases. The ulcer was gastric in nearly two-thirds of the instances, and duodenal in the remainder. Alternation of the two conditions occurred in the majority of patients (sometimes with a triple alternation involving an eczema), but a sizable proportion had both conditions simultaneously. It was claimed that therapy of the asthma by means of desensitization, autohemotherapy, peptones, or radiotherapy to the diencephalon, would control the peptic ulcers as well. The occurrence of peptic ulcers under steroid therapy has been mentioned earlier.

Certain schools of allergy have long speculated regarding the existence of *hepatic insufficiency* in asthma, largely because of the frequency of various digestive disorders. Turiaf, Blanchon and Morival[353] found that a battery of liver function studies in twenty-five cases of bronchial asthma with digestive complaints suggesting "hepatobiliary dyspepsia" were essentially normal, as were hepatic biopsies in ten instances and cholecystography in sixteen. These investigators blamed spasm, vascular and canalicular atony, secretory abnormalities, and inflammation of the biliary ducts for the digestive complaints, and compared the hepatobiliary changes to those in the bronchi in asthma. The digestive manifestations could be regarded as neither the cause nor the consequence of the asthma.

Concomitant *thyroid disorders* in patients with asthma are rare, according to Turiaf and Marland.[355] In 1,500 cases of asthma they found only seven instances of hypothyroidism and two of hyperthyroidism. The treatment of the latter had no influence on the asthma, but therapy of the hypothyroidism with thyroid extract always helped the asthma.

Electroencephalography in 126 asthmatic patients by Panzini[253] revealed an epileptic pattern in only three of forty-eight children and in three of seventy-eight adults. In contrast to several previous reports, he denied

the frequent concurrence of epilepsy and asthma. However, Farrerons-Co and his co-workers[90] found significant electroencephalographic abnormalities in a majority of twenty-three asthmatic children, noting particularly a tendency to "slowed hypersynchronization."

In answer to a Query,[264] is was stated that there is no known etiologic relationship between *silicosis* and asthma. However, the former condition may cause emphysema and symptoms simulating asthma, but not the true paroxysal type. There may of course be an unfavorable psychologic reaction of the asthmatic patient to exposure to any dust. On an organic basis, exposure to silica is no more harmful to an asthmatic person than to any other worker.

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818 Medical Arts Bldg.,
Philadelphia 2, Pa.

REV. WILLIAM D. O'LEARY, S.J., M.D., DIES

Rev. William D. O'Leary, S.J., M.D., New Orleans, Louisiana, died of a coronary thrombosis on February 1, 1955. Allergists and readers of the ANNALS will remember Father O'Leary for his interesting talk at the Southwest Allergy Forum in May 1954, which was published in the September-October 1954 issue of the ANNALS OF ALLERGY under the title of "Psychosomatic Symptoms from a Spiritual Viewpoint." Before entering the Jesuit Order, Father O'Leary was a practicing pediatrician in New York City, but in recent years he became interested in psychiatry. At one time he was president of Spring Hill College in Mobile, Alabama, and at the time of his death was Regent of the Loyola Dental School in New Orleans, where he also served as assistant to the dean.

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Volume 12 (1954) of the ANNALS OF ALLERGY, bound in durable green buckram, is now available in limited quantity for $12.00 per copy, postpaid.

NEW SUSTAINING MEMBERS

The American College of Allergists is pleased to call the attention of its members to two additions to the roster of Sustaining Members of the College. Barry Laboratories, Inc., of Detroit, Michigan, manufacturers of allergens, and the Ralston Purina Company of St. Louis, Missouri, makers of Ry-Krisp, have joined the many other manufacturers who give additional support to the College through this type of membership.

BOOK REVIEWS

1955 MEDICAL PROGRESS. A Review of Medical Advances During 1954. Edited by Morris Fishbein, M.D., Clinical Assistant Professor of Medicine, University of Illinois College of Medicine, Chicago, Illinois. 346 pages. New York and Toronto: The Blakiston Division, McGraw-Hill Book Company, Inc., 1955. Price $5.00.

1955 Medical Progress is the third in a series, begun in 1953, in which the advances in medicine for the year are noted and brought to the attention of the reader. In this revision many of the subjects discussed in the two previous volumes are presented by the same authors, and some subjects have been omitted and replaced by others which are more timely. In some instances, subjects previously discussed by others are handled by new authors in this issue in order that a different point of view may be expressed.

The chapter on allergy this year is written by Dr. George L. Waldbott, who presents the subject under the headings of classification, mechanism, diagnostic methods, causative substances, pollen and fungus surveys, unusual manifestations of allergy (Shwartzman phenomenon, neurologic manifestations, urticaria, complicating allergic asthma, simulating asthma), contact and atopic dermatitis, drug reactions, corticotropin and cortisone and other therapy. He includes a table showing dosages of antibacterial drugs used in aerosol therapy and lists 106 references.

In his summary of the year's progress in medicine, Dr. Fishbein states that the outstanding steps in medical progress in 1954 were: (1) the perfection of vaccine for poliomyelitis, with the mass experiment to determine its value; (2) the introduction of new drugs, including chlorpromazine, Diamox®, rauwolfia, and lysergic acid; (3) surgery of the heart; and (4) improvements in the use of the x-ray for diagnosis through the introduction of new contrast media. New antibiotics have been produced through continued research and the old ones have been improved. The editor also discusses the latest developments in vitamin therapy, treatment of rheumatic fever, dental caries, coronary thrombosis, skin disturbances, demand feeding of babies, physical therapy, and improvement in sun glasses.

Each chapter is followed by a list of current references on the subject. As before, this little volume provides an easy desk reference of the latest developments in the various fields of medicine.—V.S.

YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY, 1954-1955 Year Book Series. Edited by Marion B. Sulzberger, M.D., Professor, and Rudolf L. Baer, M.D., Associate Professor, Department of Dermatology and Syphilology, New York University Post-Graduate Medical School, and Skin and Cancer Unit and University Hospital, New York University-Bellevue Medical Center, New York, N. Y. Chicago: The Year Book Publishers, 1955. 472 pages, illus. Price $6.00.

In the twenty-four years that the senior editor has collaborated on this year book, tremendous strides have been made both in the diagnosis and in the treatment of this specialty.

This volume covers the dermatologic literature from December, 1953, through November, 1954. The authors begin with a twenty-four page review of the recent advances in dermatologic mycology, explaining that while the recent progress in modern dermatology has made possible the treatment of many more skin diseases by the nonspecialist, fungous infections of the skin comprise a large part of the practice of the specialist in dermatology. While this is not intended as an exhaustive review of dermatologic mycology, the authors point out certain recent advances in

the various aspects of such fungous diseases as dermatophytosis or fungous infection of the feet, infections due to trichophyton rubrum, tinea capitas or ringworm of the scalp, and *Candida albicans* infections. Thirty-seven references follow this review.

In ten chapters treatment and prevention are discussed, as are eczematous and atopic dermatitis, urticaria, and allergy; drug eruptions; miscellaneous dermatoses; cancers, precanceroses, and other tumors; fungous infections; other infections and infestations; venereal diseases and their treatment; investigative studies; and miscellaneous topics. As in all volumes in the Year Book Series, valuable comments by the editors follow each abstracted article.

All dermatologists, allergists, and physicians who treat diseases of the skin need this volume to bring them up to date on the diagnosis and therapy of skin diseases.

ION EXCHANGE AND ADSORPTION AGENTS IN MEDICINE. The Concept of Intestinal Bionomics. Gustav J. Martin, Sc. D., Research Director, The National Drug Company, Philadelphia, Pennsylvania. Boston: Little, Brown and Company, 1955. 333 pages, illus. Price $7.50.

The author has been investigating the medical uses for exchange resins since 1944, and into this volume he has put the results of these years of extensive research into the basic chemistry and clinical applications of ion exchange and adsorption agents. His work first resulted in the application of the anion exchangers in the treatment of peptic ulcer and the use of cation exchangers for sodium reduction. Now a more important application of these two resin types has resulted—namely, in the conditioning of the gastrointestinal tract. By this, the author says he means to "suggest a state in which toxic chemicals are retained in the intestine and beneficial and nutrient materials permitted entrance into the system. This could well be defined as differential or selective ion exchange and adsorption for medical purposes."

In this volume Dr. Martin contends that the medical history of any patient is the record of those irrevocable changes precipitated in the bodily economy, and that all chronic degenerative disease is, in part, the result of the absorption from the intestine of small quantities of toxic chemicals. He believes that proper selection of ion exchange and adsorption materials will prevent absorption of these toxins.

Each of the ten chapters is well documented with references.—V.E.S.

CLAUDE BERNARD AND THE EXPERIMENTAL METHOD IN MEDICINE. J. M. D. Olmsted, Professor of Physiology at the University of California, and E. Harris Olmsted. 277 pages. New York: Henry Schuman, Inc., 1955. Price, $4.00.

This is a competently written biography of Claude Bernard (1813-1878), now regarded as the founder of experimental medicine, by two authors, one whose scientific training and knowledge render him especially fitted to deal with the subject. This is the story of a French country boy, first apprenticed to an apothecary, who became a medical student in Paris and went on to achieve for himself a distinguished name in the field of physiology. It was not a highly dramatic life—at least not according to Hollywood standards—but one from which flowed rich contributions to the field of human knowledge. With great care for truth and accuracy, the authors describe Bernard's scientific methods and investigations concerning the pancreas, animal glycogenesis, experimental production of diabetes, the vasomotor nerves, the effects of the South American poison curare, et cetera.

Through this meticulous presentation of Bernard in the laboratory, the known facts of his personal life, his relations with contemporary scientists, with his students and friends, including Madame Raffalovich, Sainte-Beuve, his personality as an individual gradually emerges.—I.W.

THE BIOLOGIC EFFECTS OF TOBACCO WITH EMPHASIS ON THE CLINICAL AND EXPERIMENTAL ASPECTS. Edited by Ernest L. Wynder, M.D., Head, Section of Epidemiology, and Associate, Sloan-Kettering Institute for Cancer Research. 215 pages. Price $4.50. Boston, Toronto: Little, Brown & Co.

Since the tobacco question is one of the "burning" issues of the hour, this volume makes a seasonable appearance. The collaborators include such outstanding investigators as E. Cuyler Hammond, Professor of Biometry, Yale University, and Director of Statistical Research, American Cancer Society; Charles J. Kensler, Lecturer in Pharmacology, Harvard Medical School; and Irving S. Wright, Professor of Clinical Medicine, Cornell University Medical College. Chemistry, pharmacology, the cardiovascular system, neoplastic diseases, the gastrointestinal tract, allergy, and cause and effect in relation to tobacco are treated in eight separate divisions.

The purpose of the book, as stated in the Foreword, is to promote fact-finding, to assemble present knowledge, and to indicate the lines along which further knowledge may be obtained.—I.W.

THE THERAPY OF SKIN TUBERCULOSIS. Gustav Riehl, M.D., professor of dermatology, University of Vienna, director of Lupus Institute, Vienna; and Oswald Köpf, M.D., former assistant, Lupus Institute, Vienna; translated and revised by Ernest A. Strakosch, M.D., director, department of dermatology, Presbyterian Hospital, Denver, Colorado. Springfield, Illinois: Charles C Thomas, Publisher, 1955. 247 pages. Price $6.75.

This little volume in the Bannerstone Division of American Lectures in Dermatology is written mainly for dermatologists and those interested in tuberculosis. It is concerned mainly with the clinical use of vitamin D_2 in skin tuberculosis. Treatment technique is discussed, as are contraindications and toxic manifestations, the action of vitamin D therapy on other forms of skin tuberculosis besides lupus vulgaris, the influence of vitamin D_2 on non-cutaneous forms of tuberculosis and other diseases, the biologic action of vitamin D, the use of antibiotics, paraminosalicylic acid, isonicotinic acid-hydrazid, and combination chemotherapy. Physical methods of therapy are discussed, including general irradiation and chemical cauterizing methods, as well as surgical procedures.

Tuberculosis of the skin is rare in the United States; therefore, this volume which gives the experiences of European dermatologists is especially valuable.

The thirty-four pages of references at the end of the book are of great value in themselves.—V.E.S.

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saccharide is found in the gamma globulin fraction of plasma. It is important to note that the gamma globulin has an inhibitive effect upon the alpha fraction which carries the agent of delayed type reactivity. This may explain several puzzling features of previous investigations.

Confirmation of these observations and their extension to other cases of delayed type reactivity will be of great interest, because they may become of importance in the actual explanation of hitherto poorly understood phenomena.—*A.J.W.*